

EVALUATION OF LEWIS ACID CATALYSED AND OTHER NITRATION STRATEGIES FOR THE SELECTIVE NITRATION OF CRESOLS

by

Rudolf Jacob Francois van Niekerk

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Prof. B. Zeelie

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-
- My parents, brothers and sisters for all their love, support and prayers.
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SUMMARY

The nitration of m- and p-cresol was investigated under mild reaction conditions in a number of solvents; the effects of certain nitration catalysts were also evaluated. These different reaction parameters were evaluated in terms of their effect on a number of important reaction responses. Other important factors that were investigated were the manipulation of the isomer ratios by changing reaction parameters, as well as important process chemistry information, such as product distribution, isolation and purification, identification of side products formed, and evaluation of the heat of reaction.

Use was made of an experimental design system to evaluate the effect of reaction parameters on the chosen design responses. It was found that the ratio of para to ortho nitrocresol products could be influenced slightly by using low concentrations of nitric acid and low reaction temperatures.

A different mechanism for the formation of 2-methyl-1,4-benzoquinone (from m-cresol nitration) was proposed (compared with that previously reported), which could explain a "one mole nitric acid" pathway and the fact that only the p-benzoquinone isomer was observed.

Reaction side products were identified and found to consist of dimers of cresol and nitrocresol, which were probably the result of oxidation of the cresol, subsequent formation of a quinomethide intermediate and reaction with either the product or the substrate.

The heat of nitration was determined for various reaction systems and found to be governed by two factors, namely the actual nitration process and also an oxidation process, which is responsible for the formation of side products.

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CHAPTER 1

INTRODUCTION

1.1 CURRENT TRENDS OF THE SOUTH AFRICAN CHEMICAL INDUSTRY

For a developing country, South Africa has an unusually large chemical industry, with substantial economic significance to the country. The industry is the largest of its kind in Africa, and differs from the other African chemical industries in that it is largely based on coal, which is used as a feedstock for its extensive synthetic fuels industry.

The chemical industry in South Africa has a relatively long history having been founded in 1896 to meet the demand for explosives for the mining industry. The discovery of diamonds near Kimberley, gold on the Witwatersrand and coalfields around Witbank and Vryheid, led to a blossoming mining industry and an increasing demand for explosives. The next 50 years saw diversification into the manufacture of inorganic acids, fertilisers and mining chemicals.

Since South Africa is a country with no proven oil reserves, little natural gas and an abundant coal resource, it is not surprising that the gasification of coal became a major factor in the development of the industry. The establishment of the petrochemical industry can be traced to when the first oil-from-coal plant was commissioned in Sasolburg in the early 1950's. However, it was only during the sixties that it became possible for an organic chemical industry, based on local raw materials and feedstocks, to become a reality. This development was further driven by the establishment of two large oil-from-coal plants at Secunda during the early 1980's to provide self-sufficiency in fuels. The synfuel sector serves not only the local petroleum industry as a fuel source, but has now become the major source of chemical feedstock and intermediates.

The chemical industry in South Africa has also been shaped by the political and regulatory environment which prevailed from 1948 to 1994. This created a philosophy of isolationism which, in turn, fostered an inward approach with the focus on import replacement. This encouraged the building of smaller scale plants with capacities to satisfy the local markets. Plants were constructed close to the inland coalfields, which had the added benefit that chemical plants were located close to the heavily populated Gauteng area, the largest domestic market. After South Africa's re-admittance to the world markets, this strategy has changed since smaller plants are not very competitive in the global market, because of the economics of scale and high transport costs. The local chemical industry is now focusing on the need to be internationally competitive and the industry is re-shaping itself accordingly.¹

The South African chemical industry may be divided into three sectors: primary (feedstocks and commodity chemicals), secondary (intermediate chemicals) and tertiary products (speciality chemicals). SASOL, AECI and Dow Sentrachem dominate the primary and secondary sectors, and they have recently diversified and expanded their businesses to include tertiary products as well. Indeed, these three companies have dominated the South African chemical industry since the eighties.

Over the past five years there has been a significant change within the South African chemical industry with company mergers and rationalisation being the order of the day. SASOL has been involved with a number of projects requiring huge amounts of capital, designed to improve their range of products as well as the quality and quantity. More international companies trading on the African continent inspired this move. In 1998, the Competitions Board rejected a bid by SASOL to take over AECI. SASOL has recently announced that it will go ahead with the building of a "world-scale" n-butanol plant at either Sasolburg or Secunda. The plant is expected to go into production during 2002. This is in addition to the detergent alcohol plant that will be built in Secunda at an estimated cost of R1bn. SASOL has also expanded their international sales-network and has opened offices in Asia, Europe and North America. SASOL

manufactures more than 200 fuel and chemical products and export their products to more than 70 countries around the world.²

AECI has undergone significant changes in recent times. They sold their interest in Polifin to SASOL in 1999, and have been in the process of discarding their fertiliser business with the sale of their 50 percent share of Kynoch. They have also recently entered into a joint venture with an American company, PPG Industries, to further develop their range of technical paints manufactured by Dulux.

In 1997 Sentrachem, another of the South African chemical giants, was taken over by the Dow Chemical Company. This buy-out came at a time when Sentrachem's profitability was extremely low due to prolonged droughts, high interest rates, increasing international competition and the plunging value of the rand. Sentrachem was in the process of rationalisation when Dow successfully acquired control. Since then, Dow has changed the appearance of the company significantly with the purchase of Hoechst's shares in Safripol. Sanachem has been restructured and is now trading under the Dow Agrosiences umbrella, the focus being export of speciality chemicals such as herbicides and pesticides. Dow Sentrachem have also entered into a joint venture with Bayer, named Chrome Chemicals, with the construction of a "high-tech" plant near Newcastle to produce value-added chrome chemicals. The Dow Chemical Company is currently the second largest US investor and has indicated that it would seek further investment opportunities in South Africa. The group has moved its Middle-East-Africa headquarters from London to Johannesburg.³

The changes that the industry has seen in recent years seem to be only the tip of the iceberg, with international competition becoming tougher all the time. The only way for the medium-to-large sized company to survive is to become bigger by continually incorporating its competitors into its own structures. Another strategy, for large companies, is to trim their businesses and to discard all non-core business. The result is that a number of large corporations are established

that have interests in a number of markets, but only trading in products that form the core of their business.

Producers of commodity chemicals are now also diversifying and becoming involved with the production of valuable downstream products. These companies make use of their own feedstocks to produce the high-priced speciality chemicals, instead of selling the low-valued bulk chemicals. A term has been coined to describe the current trends in manufacturing markets; this is known as “globalisation” of markets. These trends are not new to the world and have been in operation for years. It is, however, a relatively new concept in South Africa. This process is also still far from being over since companies must remain competitive. South Africa is seen as the leader of Africa and because of previous political isolation, is still a relatively untapped market. For this reason, big companies such as Dow have been establishing a foothold in Africa. It is their hope that South Africa will open the door to the rest of the continent. International investment in this country has, however, been very slow due to the unstable socio-economic situation in the country with its unusually high crime, unemployment and illiteracy figures.

This trend of market globalisation has allowed small companies to manufacture high-value low-volume speciality products for the domestic market, which cannot be produced cost-effectively by the major players in the world chemical industry. Examples of such efforts are the small-scale production of animal feeds, fertilisers and the formulation of lubricants for the local rubber industry. The production of low-priced detergents, soaps and softeners for the predominantly black market is also a result.

It is thus apparent that the South African chemical industry is undergoing a metamorphosis and might emerge a more streamlined industry. Opportunities have presented themselves to the small chemicals producer as well as the corporate giant. If the instability in the country comes to an end, the possibility exists that the South African chemical industry may experience a sudden growth explosion.

1.2 CHEMICALS FROM COAL

As mentioned above, South Africa is a country that has no significant natural oil or gas fields. During the years of political isolation, it became necessary for the country to investigate the possibility of using low-grade coal, one of the few abundant natural resources in South Africa, to produce oil and other chemical feedstocks. The oil would be used to produce fuel for the local market and feedstocks for the South African chemical industry. It is thus that the Government-sponsored South-African Coal Oil and Gas Corporation (SASOL) was established and obtained licenses to operate plants for the production of synthesis gas from coal and the Fischer-Tropsch process, as well as a process which was based upon the American Hydrocol process. Both these processes were used; the former to produce high proportions of medium-octane petrol, light petroleum gas and a range of chemicals, and the latter to produce mainly higher boiling waxes, oils and diesel.^{4,5}

The production of coal gas on large-scale brought with it the problem of how to dispose of the coal tar formed as by-product. Although coal tar has been distilled for many years, it was previously used as a waterproof application and later for creosoting railway sleepers. The rapid growth of the organic chemical industry soon indicated that coal tar was a valuable source of new chemical substances, benzene, phenol, aniline, naphthalene, toluene, anthracene and the cresols all being eventually isolated from it.^{6,7}

When coal is heated to 1000°C, in the absence of air, coke is formed with a number of liquid and gaseous decomposition products. Coke is almost pure carbon, and is used in the manufacture of steel.⁸ After the coking process, the liquid and gaseous by-products are condensed to form the coal tar. The liquid by-products include an aqueous phase containing ammonia and an organic phase; the phases are subsequently separated and the organics are distilled into a number of crude fractions. The aqueous phase is steam-distilled to liberate ammonia, which is recovered in the form of ammonium sulphate for the fertiliser market.⁹

The coal tar, an extremely complex mixture of organic compounds, is normally separated by distillation, to afford a number of fractions of tar oils and a pitch residue. The number of fractions and their content depend on the temperature at which the carbonisation was carried out. Tars that were obtained at relatively low temperatures (420°C) contain particularly high amounts of phenolics, but little benzene and naphthalene.⁷

In general, the main tar fractions obtained at the specified temperature ranges have the following composition:

- Light oil
(Up to 170°C)
Contains mainly crude naphtha with some benzene, toluene and xylene. These are mainly used as solvents for paints and polishes, although benzene is also used in explosives, saccharine and polyurethanes. The light oil fraction is small since most of the low boiling hydrocarbons remain entrained in the coal gas and are removed during the gas-oil washing stage.
- Middle oil
(170-230°C)
Originally this lower boiling fraction was known as “carbolic oil” and contains mainly phenol, cresols and the xylenols. These compounds are used as disinfectants and in the production of resins and plasticisers. Phenol is used in the synthesis of aspirin and nylon. The high boiling fraction is mainly used in the production of insect repellent and is also useful in the manufacture of dyestuffs and resins.
- Heavy oil
(230-270°C)
This fraction contains a high proportion of “creosote”, a blend of high boiling tar oils from which valuable components such as anthracene and tar acids and bases have been removed. Mixtures of pitch and creosote produced from

this fraction are used as liquid coal tar fuels for heating furnaces. Creosote oils are also widely used for preserving wood and in the formulation of sheep dips and fruit sprays. During World War II, creosote was hydrogenated to produce petrol.

- Anthracene oil
(270-350°C)

This fraction contains very small quantities of anthracene and phenanthrene, which are removed as crude coke by cooling and filtering. Anthracene is used in the manufacture of dyestuffs based on anthraquinone. The other components are heavy coal tar fuels and road tar.

- Pitch

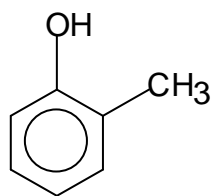
The pitch residue is used as a fuel, as a binding agent for the production of smokeless fuel briquettes, weather-proofing roofs, and for the manufacture of anti-corrosion metal-paints.⁷

1.3 CRESOLS

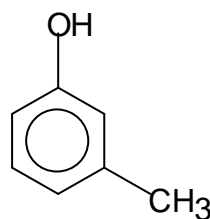
Cresols are important chemical raw materials, which were originally obtained only from coal tar in the coal-gasification process; after World War II, they were also obtained from spent refinery caustics. Since 1960, they have been produced synthetically on a much larger scale than that obtained from natural sources, i.e. cresol from coal tar.

Cresol and its derivatives are widely distributed in nature. They are produced as metabolites of various micro-organisms and are found in the urine of mammals. Humans eliminate approximately 87 mg of p-cresol per day in their urine. Cresol is also found in small amounts in certain foods and drinks; it is found in tomatoes, cheeses, coffees and teas.⁹

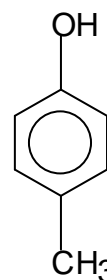
Cresol, also named methylphenol, with formula C_7H_8O and molecular weight 108.14, occurs in three isomeric forms:



o-cresol
2-methylphenol
[98-48-7]



m-cresol
3-methylphenol
[103-39-4]



p-cresol
4-methylphenol
[106-44-5]

1.3.1 Physical properties

As pure substances, o- and p-cresol are crystalline; m-cresol is a viscous oil at room temperature. The cresols have a phenolic odour and are colourless, but discolour to become yellow or brown with time. Cresols absorb moisture from the air since water dissolves very easily in them. The solubility of cresol is high in many organic solvents such as aliphatic alcohols, ethers, chloroform and glycerol. They are less soluble in water than phenol. The presence of water-soluble organic substances, such as methanol, raises their solubility in water. Dissolved inorganic salts lower the solubility of cresol in water.⁹ Other physical properties of the cresols are summarised in Table 1.1 below.

Table 1.1: Some physical properties of the cresols

Property	o-Cresol	m-Cresol	p-Cresol
Melting point at 101.3 kPa, (°C)	30.99	12.22	34.69
Boiling point at 101.3 kPa, (°C)	191.00	202.23	201.94
Density at 25°C, (g/cm ³)	1.135	1.030	1.154
Dielectric constant at 50°C	6.00	9.86	10.18

1.3.2 Chemical properties

Chemically, the cresols are similar to phenol. These compounds are weak acids and dissolve in aqueous alkali solutions to form cresolates. They can thus be extracted into sodium hydroxide solution from solvents that are not miscible with water. Their acidity is, however, so low (pK_a 10.1-10.3) that they may be liberated by hydrogen sulphide (pK_a 7.2) and carbon dioxide (pK_a 6.4) from cresolates. Therefore, they hardly dissolve in solutions of sodium carbonate or sodium hydrogen carbonate.⁹

Cresols, like phenol, undergo electrophilic substitution reactions. The electrophile normally attaches to the aromatic nucleus in the o- and p-positions relative to the hydroxyl group. The cresols can therefore be nitrated in even dilute nitric acid; nitrosation, sulphonation and alkylation also readily occur. Electrophilic substitutions are occasionally complicated by the formation of the cyclohexadienone intermediate after addition of the electrophile.

1.3.3 Sources

Cresols have a number of sources which may be separated into two main groups, namely, "natural" sources and "synthetic" sources. One "natural" source is the isolation of cresols and xylenols from coal tars which are obtained in high-temperature coking, low-temperature carbonisation and Lurgi pressure gasification of coal processes, as applied by SASOL; another "natural" source of the cresols is spent refinery caustics. "Synthetic" sources refer to production processes that were established to produce cresol in large enough quantities to satisfy the increasing demand in these compounds.

1.3.3.1 Isolation from coal tars

The content of the phenolic compounds that may be isolated from coal tar is heavily dependent upon the process employed. For instance, the high-temperature coke-oven tar, obtained in the production of metallurgical coke from bituminous coal at 900-1300°C, contains approximately 0.4-0.6 wt % phenol, 0.8-1 wt % cresols and 0.2-0.5 wt % xylenols. Approximately 10 times more $C_6 - C_8$ phenols are isolated from coal tars obtained from the low-temperature

carbonisation and the Lurgi pressure gasification. The phenols may be isolated from the tar by extraction with sodium hydroxide or from the carbolic oil fraction, which boils at 180-210°C.⁹

The scale of cresols and xylenols recovery from coal tars has been continually decreasing over the past two decades. The primary reason for this decrease is the fact that the consumption of the iron- and steel-producing industry, chiefly responsible for the production of coal tars, has been declining. Processes that lead to lower phenolics-containing tars have been used increasingly. The situation may change when the gasification of coal once again becomes the main source of syngas for the petrochemicals industry, as the price of natural gas rises.

1.3.3.2 Recovery from spent refinery caustics

This method of cresol isolation is mostly employed in the United States. The cresols and xylenols are obtained from the naphtha fraction produced in catalytic and thermal cracking processes in the petrochemical industry. During the removal of sulphur compounds contained in these fractions by scrubbing with concentrated alkaline solutions, the phenolic compounds are extracted. The phenols are then precipitated from the alkaline phase in a packed column with a countercurrent stream of carbon dioxide and decanted. The phenols still present in the carbonate/ hydrogen carbonate phase are extracted with an organic solvent, and then again extracted into the alkaline aqueous phase, which is then returned to the column. A typical composition of the phenol mixture obtained in this way is approximately 20 % phenol, 18 % o-cresol, 22 % m-cresol, 9 % p-cresol, 28 % xylenols and 3 % higher phenols. This mixture is then separated by distillation into phenols, o-cresol, a m-/ p-cresol mixture and the xylenols.⁹

1.3.3.3 Methods of production

Cresols are currently produced in the following processes:

- Alkali fusion of toluene sulphonates,
- Alkaline chlorotoluene hydrolysis,
- Rearrangement of cymene hydroperoxide,
- Methylation of phenol in the vapour or liquid phase.

The first three processes are based upon a method for producing phenol from benzene, but use toluene as starting substrate. The methylation of phenol is a process that was developed specifically for the production of cresols.⁹

1.3.4 Separation of cresol mixtures

Since the difference in boiling point of m- and p-cresol is so small, distillation of a mixture of the isomers of cresol only yields pure o-cresol and a mixture of the other two isomers. m-Cresol and p-cresol may even be obtained as one boiling fraction when the distillation is carried out under reduced pressure. Thus other methods had to be developed to separate mixtures of m- and p-cresol. These are summarised in Table 1.2:

Table 1.2: Methods of separation of m- and p-cresol⁹

Separation Method	Description
Physicochemical Processes <ul style="list-style-type: none"> <li data-bbox="267 474 516 506">• Crystallisation <li data-bbox="267 806 467 837">• Adsorption <li data-bbox="267 1083 526 1115">• Other Methods 	<p data-bbox="581 474 1401 726">It is possible to obtain pure p-cresol from mixtures containing more than 58 % p-cresol at normal pressure, and m-cresol from mixtures containing more than 89 % m-cresol. Applying pressure can extend the range of the p-cresol crystallisation.</p> <p data-bbox="581 806 1401 999">Certain zeolites adsorb p-cresol more strongly than m-cresol. Thus one can separate a mixture in an adsorption column and subsequent desorption with a suitable desorbing liquid such as an aliphatic alcohol or ketone.</p> <p data-bbox="581 1083 1401 1213">These methods include azeotropic distillation with benzyl alcohol or countercurrent extraction with selective solvents.</p>
Formation of Addition Compounds	<p data-bbox="581 1245 1401 1333">Mixtures of m- and p-cresol may be separated by formation of thermodynamically stable adducts.</p> <p data-bbox="581 1354 1401 1386">p-Cresol is separated by addition of calcium bromide.</p> <p data-bbox="581 1407 1401 1495">m-Cresol selectively forms adducts with sodium acetate or urea.</p>

Table 1.2: continued...

Separation Method	Description
Ester or salt formation	The mother liquor, enriched with p-cresol by the precipitation of the m-cresol adduct with sodium acetate, can react with oxalic acid to give the semi- or di-ester, which is precipitated at 20°C. The precipitate is hydrolysed to give almost pure p-cresol.
Nuclear Substitution Methods	Mixtures of m- and p-cresol react with isobutene to form 2,6-di-tert-butyl-p-cresol and 2,4-di-tert-butyl-m-cresol, which are easily separated by means of distillation. p-Cresol, m-cresol and isobutene are recovered after the dealkylation of these di-tert-butylcresols. The individual cresols are then further purified by distillation and may ultimately have a purity higher than 99 percent.

1.3.5 Uses

1.3.5.1 o-Cresol

Most of the o-cresol manufactured in Europe is chlorinated to produce 4-chloro-o-cresol (PCOC), which is used in the production of various chlorophenoxyalkanoic acids, such as 4-chloro-2-methylphenoxyacetic acid (MCPA); these compounds are important as selective herbicides. A much smaller proportion of o-cresol is nitrated in the production of DNOC (4,6-dinitro-o-cresol), which has both insecticidal and herbicidal properties. Highly pure o-cresol produced in Japan is used for the production of epoxy-o-cresol novolak resins, which are used as sealing agents in the manufacture of integrated circuits. o-Cresol also serves as a precursor for various dye intermediates; o-cresotinic acid (o-hydroxymethylbenzoic acid) is the most important and is produced by the Kolbe synthesis. In fact, o-cresotinic acid is further used in the production of various pharmaceutical products. The carbonate ester of o-cresol is used as the starting material for the synthesis of coumarin, while the alkylation of o-cresol with propene gives carvacol (5-isopropyl-2-methylphenol) used in antiseptics and

fragrances. *o*-Cresol is also used in small amounts to produce various antioxidants.⁹

1.3.5.2 m-Cresol

m-Cresol, either pure or mixed with *p*-cresol, is used as the starting material of important insecticides such as *O,O*-dimethyl-*O*-(3-methyl-4-nitrophenyl)-thionophosphoric acid ester (fenitrothion) and *O,O*-dimethyl-*O*-(3-methyl-4-methylthiophenyl)-thionophosphoric acid ester (fenthion). In addition, *m*-cresol is required as starting material for the production of *m*-phenoxytoluene which, after oxidation to *m*-phenoxybenzaldehyde, serves as an important precursor in the production of pyrethroid insecticides. *m*-Cresol is an important chemical in the fragrance and flavour industry, and serves as the starting material in the production of (–)-menthol. 6-*tert*-Butyl-*m*-cresol is obtained by the isobutylation of *m*-cresol, and is used as a starting material in the flavours industry and for the production of various antioxidants. In Japan, *m*-cresol is aminated to form *m*-toluidine. A number of disinfectants and preservatives are obtained from 4-chloro-*m*-cresol, which is a product of the selective chlorination of *m*-cresol. 2,4,6-Trinitro-*m*-cresol has been used as an explosive.⁹

1.3.5.3 p-Cresol

p-Cresol, pure or mixed with the meta-isomer is used for the production of 2,6-di-*tert*-butyl-*p*-cresol (BHT), a widely applicable antioxidant. 2-Alkyl-*p*-cresols, which are produced through the monoalkylation of *p*-cresol and further condensed with formaldehyde or sulphur dichloride, are also fairly important as antioxidants. It is used extensively in the fragrance and flavour industry to produce *p*-anisaldehyde from *p*-cresol methyl ether. As with *o*- and *m*-cresol, the para isomer is also used as dye components.⁹

1.3.5.4 m-/ p-Cresol

Mixtures of the isomers (free from the *o*-isomer) are used to produce tricresyl phosphate and diphenyl cresyl phosphate, which are useful as fire-resistant hydraulic fluids, lubricant additives, air filter oils and as fire-retardant plasticisers

for PVC. Cresols have fungicidal properties and have thus found application as soap disinfectants. Crude cresols are used as wood preservatives. Cresol mixtures are also used in ore flotation and fiber treatment, and as a metal degreasing and oil-cutting component. Methylcyclohexanol and methylcyclohexanone are produced by the hydrogenation of cresols and are used in the paint and textile industries.

1.4 NITROCRESOLS

Many mono- and dinitrocresols are available, but only those that may be prepared easily and economically by either nitration or nitrosation of readily available cresols, are significant. The next most accessible route to nitrocresols is by diazotization of nitrotoluidines. Some phenols with higher alkyl groups are readily available and certain of their nitro-derivatives are used as agrochemicals.

1.4.1 Physical properties

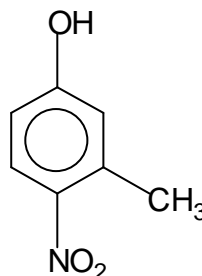
Compounds of this group are all yellow solids at room temperature with melting points ranging between 33 and 146°C. Boiling points are generally high with decomposition occurring at atmospheric pressure. Steam-distillation provides a method of separation and purification for some of these compounds. Some of these compounds are explosive and most decompose violently with the formation of nitrous vapours. They are all extremely soluble in solvents such as petroleum ether and toluene and some have a limited solubility in water. All may be crystallised as either prisms, plates or needles from a variety of solvents.^{10,11} Table 1.3 highlights the more important nitrocresols and their physical properties.

Table 1.3: Some physical properties of the more important nitrocresols.

Property	4-Nitro-m-cresol	2-Nitro-p-cresol	4,6-Dinitro-o-cresol	2,6-Dinitro-p-cresol
Melting point (°C)	128-129	33	86.5	82
Boiling point (°C)	>200 at atm. decomp.	125 (2.9 kPa)	-	-
Solubility in water	sparingly	sparingly	sparingly	-

1.4.2 Uses

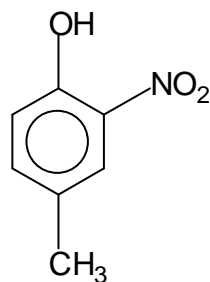
1.4.2.1 4-Nitro-m-cresol



3-methyl-4-nitrophenol
[2581-34-2]

This compound is used in the production of the derived insecticide metathion (fenitrothion), which is an analogue of methyl parathion and less toxic.⁹ Methyl parathion is a powerful restricted-use substance used on cotton, rice, soybean and some vegetables. It is very effective against cockroaches.^{12,13}

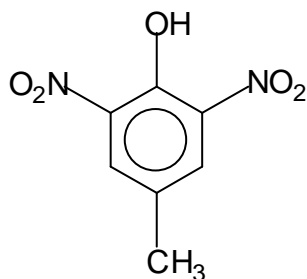
1.4.2.2 2-Nitro-p-cresol



4-methyl-2-nitrophenol
[119-33-5]

An aqueous alkaline solution of 2-nitro-p-cresol is treated with methyl chloride under pressure to give the methyl ether, which is then reduced in the presence of iron to cresidine, a compound used in the production of various dyes and pigments.¹⁰

1.4.2.3 2,6-Dinitro-p-cresol



4-methyl-2,6-dinitrophenol
[609-93-8]

This compound has found use as an insecticide exhibiting properties similar to the more widely used DNOC (4,6-dinitro-o-cresol).¹⁰

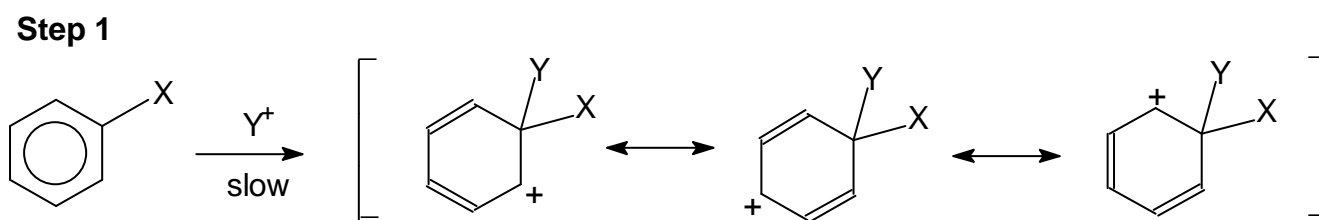
1.5 NITRATION

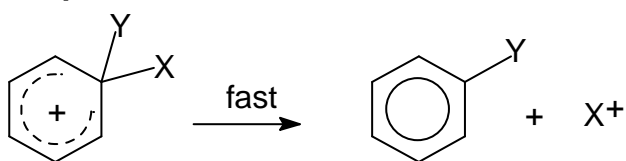
1.5.1 General properties of nitroaromatic compounds

Most nitroaromatic compounds are yellow crystalline solids; a few of these compounds, such as nitrobenzene and some of the nitrotoluenes, are yellow liquids. Many of these compounds are steam volatile; in fact, with the exception of a few of the mono-nitro derivatives, they cannot be distilled at atmospheric pressure since they violently decompose upon heating. All nitroaromatics are denser than water and are relatively insoluble in water. However, they dissolve in a wide number of organic solvents. The nitro group is firmly attached to the aromatic nucleus and may only be replaced under certain conditions. The most important reaction that they undergo is reduction with the aid of a number of reducing agents. Grignard reagents attack the nitro-group, and thus nitro-substituted aryl halides cannot be used for the preparation of these compounds.

1.5.2 The mechanism of nitration

Nitration of an aromatic nucleus proceeds via an electrophilic substitution mechanism. The electrophile may be a positive or a dipole. If it is a positive ion, it attacks the ring removing a pair of electrons from the sextet to give a carbocation. The Wheland intermediate, or arenium intermediate, formed by this first step has three resonance hybrids and is relatively unstable. The most likely method for the carbocation to stabilise itself is by the loss of a proton. The second step, whereby the sextet is restored, is nearly always faster than the initial attack by the electrophile.¹⁴

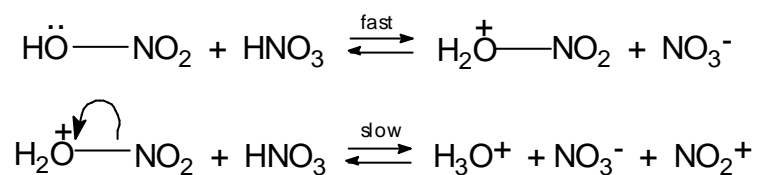


Step 2

Aromatic nitration appears to be the aromatic substitution reaction which has been studied most closely.^{15,16} Preparative nitration is normally carried out in mixed acid, which is a mixture of concentrated nitric and sulphuric acids. The explanation for the presence of the sulphuric acid was that it effectively removed the water formed in the actual nitration reaction. However this view has subsequently changed. It is now believed that sulphuric acid catalyses the formation of the nitronium ion (NO_2^+), which is the electrophile species that is directly responsible for the electrophilic substitution.¹⁷ The nitronium ion is formed in concentrated sulphuric acid according to the following equation:



The existence of the nitronium ion has been determined spectroscopically with a line at 1400cm^{-1} in the Raman spectrum, which indicates the presence of a species that is both linear and triatomic.¹⁷ Nitric acid is converted almost entirely to the nitronium ion in concentrated sulphuric acid and there appears little doubt that this is the species active in the electrophilic substitution process. The sulphuric acid thus provides a highly acidic medium where the NO_2^+ may be released. This fact has indeed been observed with strong acids such as HClO_4 and HF being very effective. The poor performance of nitric acid on its own in nitrating benzene can thus be explained by the lack of available NO_2^+ ions, the small amount of nitronium ions present due to a two-stage process, which may be illustrated as follows:

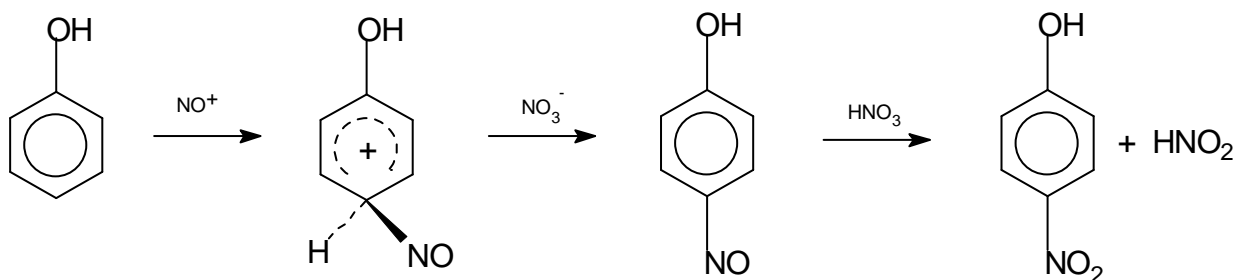
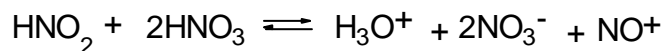


Aromatic nitrations are generally slowed down by the addition of nitrate since the substrate and NO_3^- would compete for the available NO_2^+ ions. It is thus expected that any compound that is capable of forming nitrates when added to the nitrating mixture will lower the rate. Nitrous acid is known to be almost completely ionised in concentrated HNO_3 . It is thus not surprising that nitrations carried out in pure nitric acid or in other organic solvents are generally decelerated by the addition of pure nitrous acid or nitrites, this action being similar to that which would result from the addition of any strong base. However, highly activated aromatic compounds such as phenol are found to undergo nitration readily in even dilute nitric acid, and this occurs at a far higher rate than can be explained on the basis of the NO_2^+ that is present in the mixture.¹⁷

1.5.3 Nitration via nitrosation

This effect is observed almost exclusively with highly activated aromatic substrates, such as phenol and mesitylene. These substrates are known to undergo nitrosation by nitrous acid, resulting in a nitroso-aromatic, which is known to be rapidly oxidised by nitric acid to the corresponding nitro compounds.¹⁸ The reason why this mechanism (nitrosation) has only been observed for the more reactive aromatic compounds is twofold:

- The NO^+ ion is a weaker acid and thus a much less powerful reagent in electrophilic substitutions than is the NO_2^+ ion.
- Substantial quantities of NO^+ ions may exist in solutions in which only small amounts of NO_2^+ ions are present.¹⁸



The nitrosophenol, which may be isolated, is oxidised very rapidly by nitric acid to yield the p-nitrophenol. Nitrous acid is generated in this step and the process becomes gradually faster. No nitrous acid need be present initially in the nitric acid, since a small amount of the latter attacks phenol oxidatively to yield HNO_2 . The rate-determining step is again believed to be the formation of the intermediate carbocation. At the same time, direct nitration via the NO_2^+ ion takes place, the conditions of the reaction medium determining the favoured route.

1.5.4 Reactivity and orientation in nitrations

When a mono-substituted benzene derivative, $\text{C}_6\text{H}_5\text{Y}$, undergoes electrophilic attack, the incoming substituent will be incorporated on the ring at either the ortho-, meta-, or para-position relative to the existing substituent. The rate of this reaction will take place faster or slower than with benzene itself. Substitution takes place either predominantly at the m- position or predominantly at the o- or p-positions. Formation of the m-isomer is always slower than with benzene; the formation of the o- or p-isomers is usually faster than with benzene itself. The existing substituent, Y, directs substitution on the basis of electronic effects. It can, of course, also have steric influence, but this effect would be observed mostly at the o-position. Substituents, Y, may thus be classed as either being m-directing, or o-/ p-directing; if substitution occurs faster than with benzene they are termed activating; if slower, they are said to be deactivating.^{19,20} The rates vary due to the substituent Y either adding electron density to the π -ring system

(activating) or alternatively withdrawing electron density (deactivating). This effect is thus governed by the inductive effect. There is, however, another electronic effect, known as the resonance effect, whereby electrons from the π -ring system may be delocalised over the substituent as well as the ring, forming a partial positive charge on the ring. Nitration of nitrobenzene, where Y is NO_2 , is found to result in a mixture of 93 % m-, 6 % o- and 1 % p-isomers; i.e. NO_2 is classed as a meta-directing (deactivating) substituent. By contrast, nitration of anisole (Y is OMe) yields 56 % p-, 43 % o- and 1 % m-isomers. The -OMe group is therefore termed an o/ p-director and activates the aromatic nucleus since electrophilic attack of anisole is faster than benzene.¹⁷

1.5.5 The ortho to para ratio

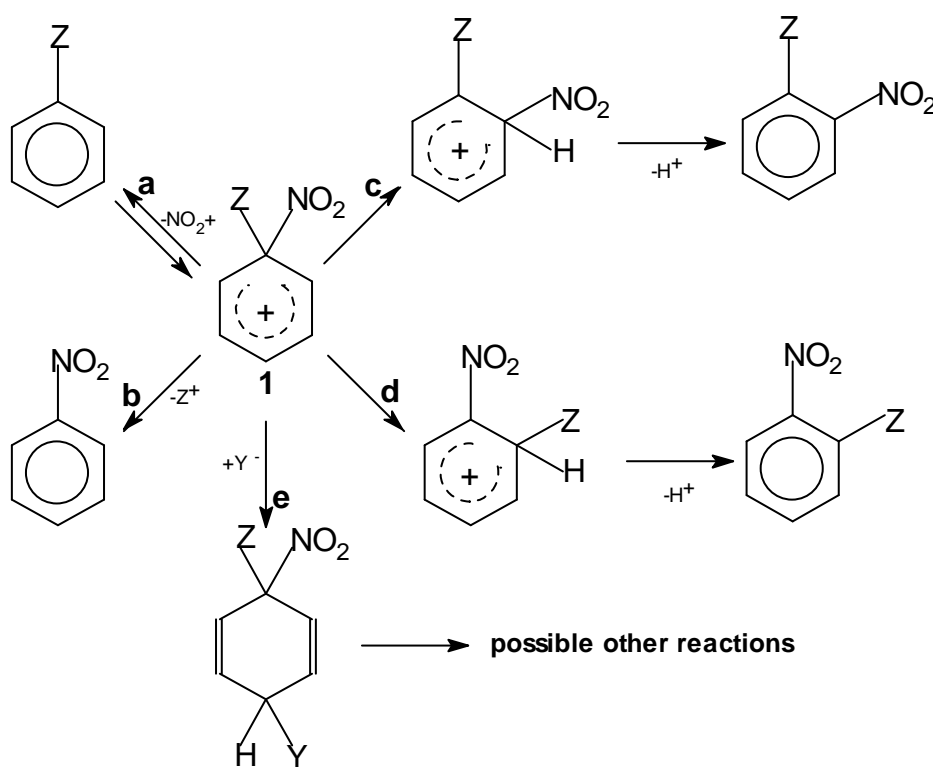
Consider for example, $\text{C}_6\text{H}_5\text{Y}$. If electronic effects alone were responsible for the position that a substituent attaches to the mono-substituted aromatic nucleus, it would be expected that the ortho to para ratio of isomers would be 2 : 1 since there are 2 ortho-sites and only one para. There are a number of reasons why this ratio is practically never observed:

- The para position is in a more favourable position for attack since the position ortho to the substituent (Y) is effectively shielded. This steric effect causes a decrease in the area through which an attacking electrophile could attach to the aromatic nucleus. It would be expected that the o : p ratio would decrease with an increase in bulkiness of the substituent, Y.
- This steric effect could however present itself in another way. The ortho to para ratio would also be expected to decrease with increasing bulk of the attacking group. For example, in the nitration of chlorobenzene, the ortho to para ratio is 0.4; in the chlorination of the same substrate the ratio is 0.7.
- The strength of the inductive effect also plays a role in determining the ortho to para ratio. In the nitration of a series of halobenzenes, the o : p ratio falls from 0.70 to 0.14 as one proceeds from iodobenzene to fluorobenzene.

- There are some cases where ortho-substitution takes place with almost the total exclusion of any para attack. It has been suggested that groups such as CHO, COOH and NO₂ facilitate nitration at the ortho position by dipole-dipole interaction with the incoming nitronium ion.
- The solvent in which the reaction is carried out also influences o-/ p-ratios. This may arise from changes in the relative stabilisation by solvent molecules of the transition states for o- and p- attack, but may also involve the actual nature of the attacking electrophile being different in different solvents.^{17,18}

1.5.6 Ipsso nitration

Ipsso attack has been studied mostly for aromatic nitrations. When NO₂⁺ attacks at the ipso position, arenium ion (1) is formed (see below), and there are at least five possible routes that this ion may then follow.¹⁴



- In path a, the arenium ion can lose NO₂⁺ and revert to the starting compound, resulting in no net reaction.

- If path b is followed, the arenium ion can lose Z^+ in which case a simple aromatic substitution with leaving group other than H takes place.
- The electrophilic group can undergo a 1,2-migration, followed by loss of an aromatic proton; path c will thus result in the same product as direct nitration. It is, however, not easy to ascertain exactly how much of the ortho product is formed in this way.
- In path d, the substituent (Z) can undergo 1,2-migration, and this would also result in the formation of the ortho product, though this arrangement would become more apparent if other substituents were present on the ring.
- The arenium ion may be subjected to nucleophilic attack (path e). This would result in the formation of cyclohexadienes by 1,4-addition to the ring; further reactions are then possible.

1.6 METHODS OF NITRATION AS APPLIED TO CRESOLS AND OTHER HIGHLY ACTIVATED AROMATIC SUBSTRATES

1.6.1 Clays

Many practical problems still remain with the commercial nitration of various organic substrates. For instance, in the United Kingdom, p-nitrotoluene was obtained by the nitration of toluene but, until only recently, most of the co-formed o-nitrotoluene was believed to be worthless and discarded or burnt. The poor selectivity of the reaction meant that approximately 30 000 T per year of the para-isomer was accompanied by 60 000 T of waste isomer (o-nitrotoluene).²¹ In an age where environmental considerations could not allow such means of disposal or, for that matter, such large amounts of by-products and waste, it is clear that there is a need for better regioselective control.

Traditionally, solids, such as chromatographic adsorbents, have been used in reactions to provide a surface on which to spread out a reagent. It was found that some of these procedures provided high yields under mild conditions. The ease of reaction set-up and work up was exceptional, with the cleanliness of the reaction mixture being another advantage. Progress in surface science, availability of new solids and an improved understanding of heterogeneous catalysis has provided opportunities to design better catalysts and solid reagents. Microporous solids such as silica and alumina offer a wide range of active sites for catalysis and can mostly be regenerated if deactivated during a reaction. Solid catalysts also have other advantages. The number of diffusional encounters is increased when the adsorbate is anchored to a solid; the adsorbates migrate to active catalytic sites which lowers the activation energy. Another consequence is the restriction of angles of attack, which increases the selectivity. Further increases in selectivity might be obtained when using microporous solids such as zeolites which are shape selective.²¹

1.6.1.1 “Clayfen”

The uses of anhydrous metallic nitrates in organic nitrations have been known for a number of years.²² It was established that in some metallic nitrates, covalent bonding existed between the metal and the oxygen of the nitrate groups, which may coordinate the metal by three different modes: as unidentate, bidentate or bridging ligands. The highest reactivity was observed in the bidentate case, with the metallic centre having abnormally high coordination numbers.²³

The reactivity of the acetone solvate of iron(III)nitrate, obtained from concentration under vacuum of acetone solution of iron(III)nitrate nonahydrate, was investigated. This very unstable reagent was stabilised on a suitable solid support.

K10 clay, an inexpensive acidic industrial catalyst, was chosen as the support after trials were conducted with other clays, sand, silica gel, alumina and others. This reagent was very unstable and lost its reactivity after only a few hours with the constant evolution of nitrogen dioxide. It was applied to number of reactions

such as the oxidation of alcohols, regioselective nitration of phenols and the conversion of thioketones into ketones.²³ The nitration of phenols was carried out under very mild conditions leading to only mononitrated products with great ease of work up of reaction mixtures. The reactions were carried out at room temperature in ether. The reaction was regioselective with no meta-nitration being detected. With m-cresol, yields of 34 % para and 20 % ortho-products were observed, with one of the ortho-products being favoured with respect to the other. p-Cresol gave 58 % yield of the ortho-product.²³ This method proved very efficient in the ring-nitration of estrone, which is an important industrial reaction. "Clayfen" nitration of this substrate gave a 55 % yield.²⁴

1.6.1.2 "Claycop"

A group led by Cornelius and Laszlo²⁵ studied a wide range of aromatic substrates, from the nitration of benzene and activated aromatics through to strongly activated aromatic compounds such as phenol, cresol and anisole with K10 clay supported cupric nitrate. It was claimed that by simply varying the conditions, it was possible to drive the reaction to either mono- or polynitration. The reactions were carried out using Menke conditions, i.e. in the presence of acetic anhydride, where the likely nitrating species is acetyl nitrate. In the polynitration of benzene, significantly higher amounts of "claycop" were used, and at times, small amounts of fuming nitric acid were added with cooling to 0 – 5°C. Generally the reactions proceeded satisfactorily at room temperature with excellent yields of polynitrated products. This system was also applied to the mononitration of substrates like m- and p-cresol, phenol and anisole. For m-cresol, a yield of 90 % was obtained with a product distribution of 55 % and 15 %, respectively, for 5-methyl-2-nitrophenol and 3-methyl-4-nitrophenol. The nitration of p-cresol gave a 95 % yield with selectivity of 92 % to 4-methyl-2-nitrophenol. Nitration occurred mostly in the ortho-position with all substrates except anisole. The difference in regioselectivity when using "claycop" with acetic anhydride or "clayfen" might be due to the formation, in the former, of an intermediate ester which lowers the electronic density of the ring, particularly in the para-position, decreasing its susceptibility toward electrophilic attack.

1.6.2 Lanthanide triflates

Lanthanide(III)triflates were used in the nitration of a range of simple aromatic compounds using stoichiometric amounts of 69 % nitric acid with high yields.²⁶ The only by-product of the reaction was water and the catalyst was recycled by simple evaporation from the water phase. Lanthanides have found increasing use as mild and selective reagents in organic synthesis; particularly lanthanide(III)triflates have been used to good effect as Lewis acids in Diels-Alder, Michael, Friedel-Crafts^{27,28} and Mukaiyama²⁹ reactions.

It is well known that even small amounts of water inhibit the action of other Lewis acid catalysts, such as AlCl_3 , which is normally the catalyst of choice for Friedel-Crafts-type reactions. Lanthanide(III)triflates, however, are stable in water and therefore do not decompose under aqueous work up conditions, unlike conventional Lewis acids.

In the nitration of activated aromatic systems, such as toluene, no dinitrated products were observed. However, the catalyst failed to effect any nitration of nitrobenzene under such mildly acidic conditions. This is in agreement with the results obtained by Kawada, Mitamura and Kobayashi²⁷ which indicated that this catalytic system only works with highly electron-rich aromatics because of its low Lewis acidity. For example, while the Friedel-Crafts acylation of anisole, mesitylene and xylene proceeded readily, no acylation was observed for toluene and benzene.

It was found that the lanthanide triflate salts, after reaction and subsequent recycling, were still active for further nitrations with little loss in rate or yield, and no change in the selectivity.²⁶ The different rates obtained with various lanthanide triflates indicate that the metal centre is involved. It is well known that mixtures of nitric acid and triflic acid effect nitration,³⁰ but it seems unlikely that free triflic acid was formed since the pH of an aqueous lanthanide triflate solution was nearly neutral.²⁶

waste, the treatment of which adds to the production cost of any product. The decrease in the o : p ratio, observed for methylanisoles, was also seen for m-cresol, where the proportion of para-substitution increases from 33 to 52 % over the range 58 to 81 % sulphuric acid.³³

The system was also used, in a number of patents, as the method of choice for the nitration of certain phenol derivatives.^{34,35} Sasaki and Mukai³⁴ used this method to nitrate tri-m-cresyl phosphate to selectively produce 5-methyl-2-nitrophenol. According to them, it was possible to change the regioselectivity of the tri-m-cresyl phosphate nitration by changing the reaction conditions; it was thus possible to also selectively produce 3-methyl-4-nitrophenol.

1.6.3.2 Nitric/ nitrous acid mixtures

It has been illustrated in this discussion how nitrous acid may catalyse aromatic nitration.^{17,18} This technique was employed by Subluskey³⁶ to nitrate a mixture of m- and p-cresol. Nitrous acid was introduced into the acid mixture in the form of liquid N_2O_4 , which was condensed from cooled NO_2 gas. Cresol was added and the mixture left to react at below $5^\circ C$. The crude product was filtered as a cake, and the 3-methyl-4-nitrophenol removed by extraction and purified by crystallisation from benzene. The yield of 3-methyl-4-nitrophenol from this reaction was 65 %.

1.6.4 Nitration via nitrosation

A number of methods have described the use of sodium nitrate as the nitrating agent in the presence of a strong acid; some of these made use of sodium nitrite as a catalyst for the reaction. Presumably the addition of nitrite (NO_2^-) was involved in the formation of a nitrosating agent (NO^+).^{37,38}

1.6.4.1 $NaNO_3/ H_2SO_4$

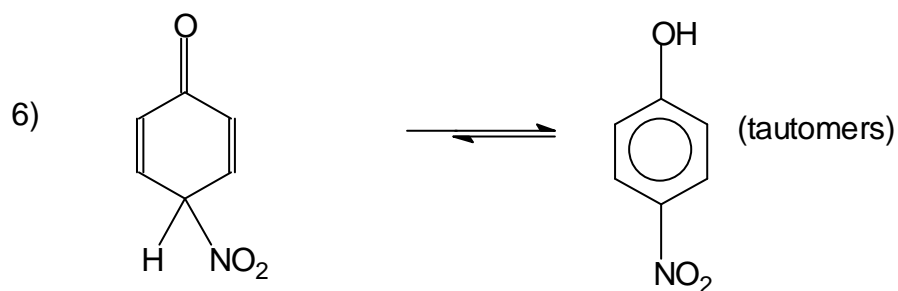
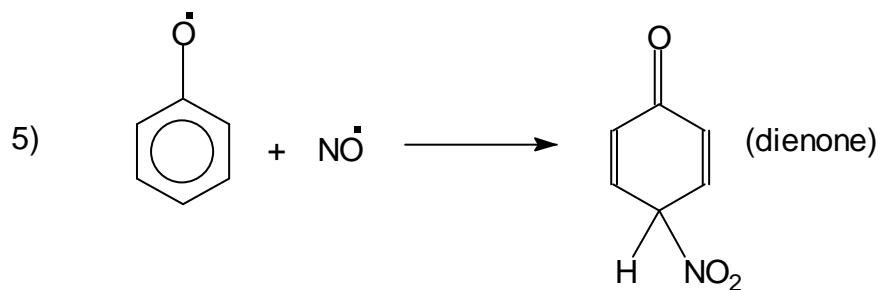
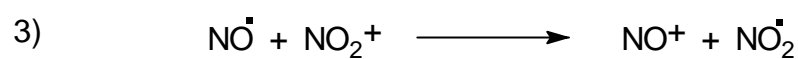
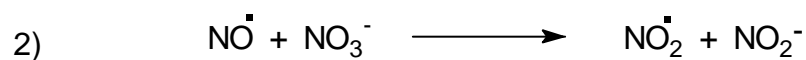
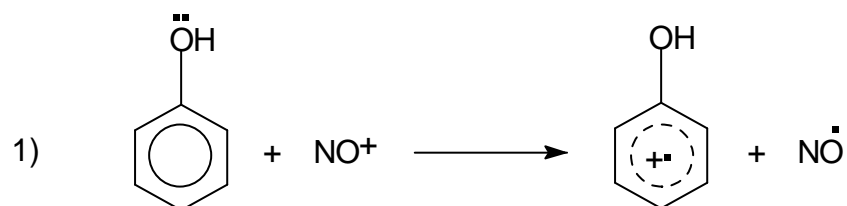
Kagan, Girard and Quertani³⁷ made use of $NaNO_3$ in the presence of hydrochloric acid with lanthanum(III)nitrate as catalyst. They claimed that the nitration of phenol only started once the lanthanum nitrate was added. It was also claimed that only two products were formed during the nitration of m-cresol; the

reaction gave a total yield of 86 %, the selectivity was 87 and 13 % respectively for 5-methyl-2-nitrophenol and 3-methyl-2-nitrophenol.

However, it has since been shown by Thompson and Zeegers³⁸ that the work done by Kagan was inaccurate. It was found that lanthanum nitrate has no catalytic influence on the reaction mixture. In addition, during the nitration of m-cresol, four products were consistently formed. The major product was the 4-nitro isomer, followed by the 6-nitro and the 2-nitro isomer, and the 2-methyl-1,4-benzoquinone by-product. The formation of the benzoquinone species had also been observed when using procedures such as dilute HNO₃, HNO₃/ AcOH, clay supported Cu(NO₃)₂²³ and NO₂/ CH₂Cl₂. No quinone was observed when nitration was carried out in 70 % H₂SO₄/ HNO₃ at 0°C, a medium in which NO₂⁺ is the dominant nitrating species.³³

Tompson et al. made use of a small excess of sodium nitrate in 3 M H₂SO₄ and a catalytic amount of sodium nitrite. This method produced excellent results in the mononitration of phenols, with yields of 90-95 % and no tarry by-products. The authors noticed the existence of an "induction period", related to temperature and acid concentration, which could be decreased by the addition of sodium nitrite. Conversely, the latency period could be increased by the addition of urea, a nitrous acid trap; the addition of one equivalent of urea completely suppressed nitration.³⁸

It was proposed that the nitration mechanism of phenols in a two-phase system proceeds through an initial electron transfer (ET) step with NO⁺ as the transfer agent, the induction period being due to slow formation of the transfer agent.

Proposed mechanism

The phenoxy radical can also undergo a second ET, a thermodynamically feasible process with NO^+ , to produce a cation. Nucleophilic attack by water would result in the formation of a hydroquinone. This in turn is readily oxidised to give the observed quinone products.³⁸

1.6.4.2 NaNO₃/ NaNO₂ mixtures

In another study, N^V and N^{III} were used as nitrating agents, where N^V is both HNO₃ and NO₃⁻ (from NaNO₃) and N^{III} is both NO⁺ and HONO (from NaNO₂) in 50 – 60 % H₂SO₄.³⁹ When only N^V was used, after 30 seconds reaction time almost no nitrophenol was formed. When using N^{III}, the reaction was practically complete in the same time period; nitrosation is rapid and yields almost entirely p-nitrophenol. Using N^V for a longer time (7 min) gave almost complete nitration; the isomer ratio changed to 0.78 : 1 (o : p), which is vastly different from that obtained by the nitrosation route (0.03 : 1). It thus seems that nitration via nitrosation exhibits an apparent preference for p-nitro products. The rate of nitrosation also seems to be higher than that of direct nitration.

1.6.5 Other innovations

1.6.5.1 Use of acetic anhydride

Various publications reported the use of acetic anhydride in the nitration mixture.⁴⁰⁻⁴⁴ The exact reason for its inclusion is not very clear as it is claimed by some that the reactive acetyl nitrate species is formed in these mixtures.⁴⁰ In contrast, others claim that it is required as a dehydrating agent, removing excess water when the reaction is carried out with dilute nitric acid.⁴²

1.6.5.2 Solvent effects

Nitrations, like many other types of reactions, may be carried out in a variety of media. Changing the solvent may, however, affect the outcome of the reaction in terms of product yields, selectivities and product distribution. For example, Germain,⁴⁴ showed that the nitration of anisole with 65 % nitric acid and sodium nitrite at room temperature gave remarkably different o : p ratios in a variety of solvents. The yields of the various reactions were also markedly different. In carbon tetrachloride, the products of the anisole nitration were exclusively ortho- or para-nitroanisoles, with

an unusual para preference (o : p = 1 : 3.7). Alkanes were found to be the most effective solvents, while no reaction was observed in diethyl ether.⁴⁴

As is the case with any other reaction type, the solvent should not react with the active species to produce side products. It is exactly for that reason that halogenated solvents, such as ethylene dichloride and ethylene trichloride, have been used frequently in these reactions.⁴⁴ Also of major importance is the fact that these solvents showed high preference for para-products. This was also observed in the case of ethyl acetate and n-butyl acetate.

1.6.5.3 Use of transfer reagents

Nitrations of aromatics have recently been carried out by the use of the nitropyridinium and quinolinium ions.^{45,46} In these cases the reaction is found to take place via a nucleophilic displacement pathway, involving the N-

nitropyridinium ions themselves and not free nitronium. It was found that steric factors, even with such bulky nitrating agents (transfer agents), did not play a major role in determining the regioselectivities.⁴⁵

In another publication, activated nitropyridinium carboxylate salts were shown to effect highly selective ortho nitration of phenol.⁴⁷ It was claimed that these highly reactive compounds could be manufactured by passing $\text{NO}_2 - \text{N}_2\text{O}_4$ gas into a solution containing the pyridinium carboxylic acid. The expensive nitronium tetrafluoroborate, the reagent normally used for these preparations, became unnecessary and the recovered pyridinium salt could be reused in further reactions.

In a separate study, use was made of nitropyrazoles as the transfer agent in the nitration of estrone. Yields were consistently in

the region of 35 – 40 %, with an apparent preference for the ortho isomer.⁴⁸

1.6.5.4 Use of gaseous reactants

The nitrations of phenols have also been carried out with gaseous reactants. Mostly these gaseous reactions are carried out with mixtures of NO_2 and N_2O_4 .^{49,50} The mechanism of these nitrations are believed to be the initial abstraction of the phenolic hydrogen by NO_2^\bullet and then reaction of the phenoxy radical with a second molecule of NO_2^\bullet . Nitrations have even been carried out with methyl nitrate.⁵¹

1.6.5.5 Side-chain nitration

Most studies on the nitration of aromatic compounds have been concerned with the electrophilic substitution of the aromatic nucleus. However, some studies have dealt with the nitration of the aromatic side-chain.⁵² Cerium(IV) ammonium nitrate has been used as a side-chain-specific nitration agent. The

mechanism seems to involve abstraction of a proton from the aromatic substituent with subsequent oxidation of the resulting benzyl radical to a cation. As is the case with other ET (electron transfer) nitration reactions, abstraction of the proton seems to be the rate-determining step.

1.7 INDUSTRIAL CONCERNS

1.7.1 Scale-up of nitrations

Safety concerns regarding the scale-up of nitrations result from a long history of safety problems associated with nitration reactions such as runaway reactions, explosions and product stability problems.

The causes leading to exothermic runaway reaction, have been identified as:

- 1. A poor understanding of the reaction chemistry, or the kinetics, leading to a badly designed plant.**
- 2. Underrated control and safety backup systems.**
- 3. Inadequate procedures and training.**

The first factor is the most important to chemists, as it is their duty to interpret the relevant reaction mechanisms.

Failure to adequately assess the process chemistry or reaction kinetics accounts for a significant number of incidents. Specific causes include:

1. An underestimation of the heat evolved.
2. Unanticipated side-reactions, including the formation of unstable by-products.
3. Changes in the onset temperature (for runaway decompositions) with varying reaction conditions.
4. Unpredicted autocatalysis.

An underestimation of the heat of reaction, prior to scale-up, caused particular problems and resulted in a number of failures. Heat dissipation from conventional laboratory glassware is generally much higher than from a full-scale reactor. This is a result of significant reductions in the surface area to volume ratio of reaction vessels with increasing size. It is therefore essential that, before scale-up, accurate information on the heat of reaction and, where appropriate, the heat generation rate be obtained so that adequate cooling can be provided. Unless this is done, the large-scale vessel may have an insufficient cooling capacity and an exothermic runaway reaction may occur.⁵³

1.7.2 Future of nitrations

With chemists under increasing pressure to perform “green chemistry”, processes are required for the selective preparation of mono- and poly- nitrated aromatic compounds. These processes must minimize the formation of by-products and large amounts of highly acidic waste. Of equal importance is the development of high yield nitration processes that are also economic in terms of capital investment as well as energy inputs. It is however a certainty that aromatic nitrations will remain one of the most important and widely used industrial synthetic methods.

CHAPTER 2

EXPERIMENTAL

2.1 MATERIALS

2.1.1 Reagents for synthesis

All materials used during the respective syntheses, together with their sources and respective grades, are listed in Tables 2.1 and 2.2 and were used as received.

Table 2.1: Organic reagents for synthesis

Chemical	Formula	Supplier	Grade/ Purity
Acetic anhydride	CH ₃ COOCOCH ₃	Saarchem	99 %
Acetone	CH ₃ COCH ₃	Riedel de Haen	99 %
Carbon tetrachloride	CCl ₄	Saarchem	99 %
m-Cresol	CH ₃ C ₆ H ₄ OH	Merck	99 %
m-/ p-Cresol	CH ₃ C ₆ H ₄ OH	Sastech	99 %
p-Cresol	CH ₃ C ₆ H ₄ OH	Aldrich	99 %
1,2-Dichloroethane	ClH ₂ CCH ₂ Cl	BDH	AR
Dichloromethane	CH ₂ Cl ₂	BDH	AR
Diethyl ether	(C ₂ H ₅) ₂ O	Saarchem	AR
Ethanol	C ₂ H ₅ OH	BDH	AR
Petroleum ether (60 – 80°C)		Saarchem	99 %
Trifluoromethanesulphonic acid	CF ₃ SO ₃ H	Aldrich	99 %

Table 2.2: Inorganic reagents for synthesis

Chemical	Formula	Supplier	Grade/ Purity
Cupric nitrate	$\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$	NT Lab Supplies	CP
De-ionised water	H_2O	BHT DSA-30 water system	<12 $\mu\text{s}/\text{cm}$
Ferric nitrate	$\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$	Merck	AR
Magnesium sulphate	MgSO_4	Saarchem	CP
Montmorillonite K10 clay		Aldrich	
Nitric acid (65%)	HNO_3	Saarchem	AR
Nitric acid (93%)	HNO_3	Protea Chemicals	CP
Sodium bicarbonate	NaHCO_3	NT Lab Supplies	CP
Sodium chloride	NaCl	NT Lab Supplies	CP
Sodium nitrate	NaNO_3	Saarchem	AR
Sodium nitrite	NaNO_2	Saarchem	AR
Sulphuric acid (98%)	H_2SO_4	BDH	AR
Yttrium carbonate	$\text{Y}_2(\text{CO}_3)_3 \cdot \text{H}_2\text{O}$	Aldrich	>99 %
Yttrium chloride	$\text{YCl}_3 \cdot 6\text{H}_2\text{O}$	Aldrich	98 %
Yttrium triflate	$\text{Y}(\text{CF}_3\text{SO}_3)_3$	Aldrich	>99 %

2.1.2 Reagents for analysis

The reagents used for HPLC analysis are listed in Table 2.3. All standard materials were used as received. Table 2.4 gives miscellaneous reagents also used for analysis.

Table 2.3: Reagents for HPLC analysis

Chemical	Formula	Supplier	Grade/ Purity
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Acetonitrile	CH ₃ CN	BDH	HPLC
2,6-Dinitro-p-cresol	C ₇ H ₆ N ₂ O ₅	Acros	95 %
2-Methyl-1,4-benzoquinone	C ₇ H ₆ O ₂	Aldrich	99 %

Table 2.3: continued...

Chemical	Formula	Supplier	Grade/ Purity
Methanol	CH ₃ OH	BDH	HPLC
3-Methyl-2-nitrophenol	C ₇ H ₇ NO ₃	Aldrich	99 %
3-Methyl-4-nitrophenol	C ₇ H ₇ NO ₃	Aldrich	99 %
4-Methyl-2-nitrophenol	C ₇ H ₇ NO ₃	Aldrich	99 %
5-Methyl-2-nitrophenol	C ₇ H ₇ NO ₃	Acros	97 %
Nitrobenzene	C ₆ H ₅ NO ₂	Merck	99 %

Table 2.4: Miscellaneous reagents for analysis

Chemical	Formula	Supplier	Grade/ Purity
Buffer solution (pH4)		Saarchem	AR
Buffer Solution (pH7)		Saarchem	AR
De-ionised water	H ₂ O	BHT DSA-30 water system	<12 µs/ cm
Di-sodium tetraborate	Na ₂ B ₄ O ₇ .10H ₂ O	Sky Chem	AR
Phenolphthalein	C ₂₀ H ₁₄ O ₄	M&B	AR
Phosphoric acid	H ₃ PO ₄	Holpro Analytics	CP

2.2 SYNTHETIC PROCEDURES

2.2.1 Preparation of reactive clays

2.2.1.1 Preparation of clay supported iron(III)nitrate – “clayfen”

Montmorillonite K10 (100 g) was added to 500 cm³ of de-ionised water and stirred vigorously for five minutes. After stirring was stopped, the mixture was left to stand for approximately one minute to allow impurities (mainly silica particles) to settle. The supernatant suspension was carefully decanted, and the washed clay separated by centrifugation. The clay was dried overnight at 120°C and stored in a desiccator.

Iron(III)nitrate nonahydrate (11.3 g; 0.028 mol) was dissolved in 190 cm³ of acetone with vigorous stirring. Montmorillonite K10 clay (15 g), pre-treated as above, was slowly added to the acetone mixture and left to stir for 12 hours. The acetone was removed by evaporation on a rotary evaporator under reduced pressure at 50°C, and the resultant solid dried under these conditions until a light yellow free-flowing powder was obtained. The “clayfen” prepared in this manner was used immediately, as the reagent is quite unstable and releases NO₂ gas constantly.

2.2.1.2 Preparation of clay supported copper(II)nitrate – “claycop”

Pre-treated montmorillonite K10 (15 g) was added to a stirred solution of copper(II)nitrate trihydrate (10.0 g; 0.041 mol) in 190 cm³ acetone and left to stir for 12 hours. The acetone was removed by evaporation on a rotary evaporator under reduced pressure at 50°C to yield a light blue free-flowing powder. The “claycop” was stored in a desiccator. This reagent is more stable than “clayfen”, and may be stored for extended periods without any obvious loss in activity.²³⁻²⁵

2.2.2 Preparation of 4-methyl-2-nitrophenol

p-Cresol (19.60 g; 181 mmol) was weighed into a 250 cm³ three-necked round bottom flask containing 150 cm³ 1,2-dichloroethane and the solution stirred at 60°C. Nitric acid (65%; 18.32 g; 191 mmol) was added dropwise over a period of 60 minutes. After the acid addition was complete, the reaction was left for an additional two hours to

ensure completion of the reaction. The mixture was then poured over ice and the organic phase extracted with petroleum ether. The excess solvent was removed by distillation, after which the crude product was weighed and set up for steam distillation with internal steam generation. The product was extracted from the aqueous phase with ether and the solvent removed by vacuum distillation. The product solidified once it cooled to yield a solid that was golden-yellow in colour with the distinct nitroaromatic odour (see Appendix 4.3 and 4.4 for GC-MS and H-NMR data).

2.3 EXPERIMENTAL PROCEDURES

2.3.1 Nitrations

2.3.1.1 Dilute nitric acid

A stock solution of the substrate (m- or p-cresol) was made in a 500 cm³ volumetric flask with the reaction solvent, 1,2-dichloroethane. This mixture also included nitrobenzene (internal standard) to facilitate later analysis. The concentration of cresol and nitrobenzene were both 0.15 mol.dm⁻³.

The stock solution was delivered from a burette into a 100 cm³ two-necked round bottom flask containing a magnetic follower. The reactor, containing 20.00 cm³ of substrate solution, thus contained cresol (3.00 mmol) and nitrobenzene (3.00 mmol). Nitric acid (65 %) was added in a 1 : 1 ratio with the substrate, using a 250 μ l microsyringe. The nitric acid (0.29 g; 0.21 cm³; 3.00 mmol) was then weighed directly into the substrate solvent mixture and a stopwatch was started. The reaction ensued immediately and the

round bottom flask was placed in a stirred oil bath, pre-heated at the specified temperature, and fitted with a reflux condenser.

Sampling was carried out prior to nitric acid addition (representing the time zero sample) and during the reaction at specified times, typically at 30 or 60 minutes. This was done by taking a 0.5 cm³ aliquot with a 2 cm³ graduated pipette. This sample was further diluted with 2.00 cm³ of acetonitrile using a burette.

2.3.1.2 Lanthanide triflate catalysed reactions

Yttrium(III)triflate (0.16 g; 0.30 mmol) was weighed into a 100 cm³ round bottom flask and 20.00 cm³ of the substrate/ internal standard stock solution was added to the reaction flask by means of a burette. The mixture was stirred for five minutes before the time (0) sample was taken. The nitric acid (0.29 g; 3.00 mmol) was weighed into the reaction mixture, timing was started and the

mixture placed in a pre-heated oil bath and fitted with a reflux condenser.

2.3.1.3 Nitrations with “clayfen”

Into a 100 cm³ two-neck round bottom flask containing 50 cm³ of diethyl ether was added 5 g of freshly prepared “clayfen”. To this suspension was added m-cresol (1.09 g; 10.1 mmol) and nitrobenzene (1.24 g; 10.1 mmol). The mixture was stirred vigorously at room temperature for 20 hours. Samples were taken periodically during the reaction to determine the progress.

2.3.1.4 Nitrations with “claycop”

To a suspension of “claycop” (2.40 g) in 30.0 cm³ carbon tetrachloride and 7.5 cm³ acetic anhydride was added m-cresol (1.09 g; 10.1 mmol) and nitrobenzene (1.23 g; 10.0 mmol). The mixture was stirred vigorously for 60 minutes at room temperature. Samples were taken at regular intervals to determine the reaction progress.

2.3.1.5 Nitration with nitric and sulphuric acid mixtures

Into a 100 cm³ two-necked round bottom flask was added 20.00 cm³ of the substrate/ internal standard stock solution. To that was added 98% H₂SO₄ (0.61 g; 6 mmol), and the mixture subsequently stirred for five minutes before an initial

sample was taken. 65% Nitric acid (0.281 g; 2.93 mmol) was added to the reaction mixture by microsyringe and timing of the reaction started. The ratio of nitric acid to substrate and nitric acid to sulphuric acid was 1 : 1 and 1 : 2, respectively. The mixture was left to react for one hour with constant stirring.

2.3.1.6 Nitrosation reactions with NaNO₂ and H₂SO₄/ or HNO₃

A series of reactions were carried out with different nitrosating mixtures. In two of the reactions, sodium nitrite was the nitrosation/ nitration agent with different amounts of sulphuric acid as the promoter. In the third, reaction sodium nitrite was added in a catalytic quantity with 65 % nitric acid.

m-Cresol and nitrobenzene in 1,2-dichloroethane (20.00 cm³) were added to the reaction vessels from a burette. To the first reaction was added NaNO₂ (0.21 g) and H₂SO₄ (0.15 g); the molar ratio of NaNO₂ : H₂SO₄ was 2 : 1.

In the second reaction, NaNO₂ (0.21 g) and H₂SO₄ (0.03 g) were again added, but, the ratio was 10 : 1 in this case.

In the final reaction NaNO₂ (0.02 g; 0.30 mmol) was added to the substrate/ internal standard mixture. Nitric acid (0.28 g; 0.20 cm³) was subsequently added to the nitration mixture.

In all three cases, mixtures were left to react for one hour with constant stirring (750 rpm) at room temperature.

2.3.2 Reaction calorimetry

A number of reactions were carried out using the HEL Simular reaction calorimeter. The data gathered from the reactions carried out on this instrument were utilised for a variety of applications and studies, from determining the heats of reaction to using the instrument to determine the efficiency of certain catalyst systems, or a tool to carry out more controlled scale-up procedures.

The system was used to automate, as well as duplicate, aspects of the nitration reactions. The nitration of p-cresol was not only carried out on this system to determine amount of energy released in the exothermic process (heat of reaction) but also because of the excellent control of experimental variables such as reaction temperature and feed rate.

The P.E. Technikon Chemistry department recently acquired the HEL (Hazard Evaluation Laboratories) non-isothermal reaction calorimetry unit. HEL Winiso control and real-time data logging software, interfaced with the power compensation interfaces, controls the instrument. A 500 cm³ stainless steel (SS316) Büchi reactor with bottom drain valve and glass insert is at the heart of the instrument. The inlet and outlet of the reactor jacket is connected to a Julabo F32 heater/ chiller unit. A Leeson, magnetic driven, impeller provides agitation. A HEL internal calibration heater with a 25 mm hot-end provides

heating from within the reactor. Liquid reagents are dosed to the reactor via a Prominent gamma G/ 4b metering pump running off a Oxford top-loader balance. Temperature differences are measured and logged in real-time at a number of key points in the reactor, for the purpose of thermodynamic calculations, by PT100 temperature probes. Provision is made on the unit for a number of additional unit operations such as on-line pH determination and adjustment, introduction of gaseous reagents via a mass flow controller, solids feed and an additional liquid feed, distillation apparatus as well as reactions under pressure (up to 50 bar).

The reaction calorimeter was operated in power compensation mode with use of the glass reaction liner. The compensation drop (the difference between the reactor temperature and jacket circulation temperature) was set between 30 and 50°C. In all cases, p-cresol was the substrate and the reaction was carried out in 250 cm³ 1,2-dichloroethane. Though there were certain changes in the reaction variables, such as acid concentration, use of a catalyst, sampling during the reaction, acid feed rate and substrate loading, a representative method may be written as follows:

p-Cresol (40.0 g; 0.370 mol) was weighed into the reactor glass liner; to this was added 250 cm³ 1,2-dichloroethane. The liner, containing the reaction mixture,

was placed inside the reactor and the reactor lid was secured on to the system. A reflux condenser fitted with a rubber hose (for venting of noxious fumes) was fitted to the reactor lid. The reactor was heated up to 50°C with the internal calibration heater with constant stirring at 500 rpm. Once stable temperature and power baseline curves were obtained, the reaction was initiated. Nitric acid (35.6 g; 25.4 cm³) was added to the reactor via the liquid dosing pump with a constant feed rate of 0.5 cm³.min⁻¹. After addition of the acid was complete, the mixture was stirred for an additional 90 minutes to ensure completeness of reaction. Samples were taken before and after the reaction by removing a 0.5 cm³ aliquot and diluting it with 5.00 cm³ acetonitrile. To that was weighed an accurate amount of the internal standard (nitrobenzene).

2.4 ANALYTICAL PROCEDURES

2.4.1 Gas Chromatography

GLC Analyses were carried out using a Varian 3400 Gas Chromatograph equipped with a 30 m x 0.32 mm i.d. SPB-1(Supelco) column, or a 30 m x 0.32 mm i.d. SPB-5 (Supelco) column, and a flame ionisation detector. Data were acquired from the detector by means of an Olirite personal computer, equipped with Delta for Windows chromatography software. The carrier gas (N₂) flow rate was 1.88 cm³.min⁻¹ with a column head pressure of 0.42 kg.cm⁻³. The injector was operated in the split mode with a split ratio of 1 : 100 with an injection volume of 1 µl. Samples were injected with the aid of a Hamilton 10 µl GC syringe. Typical GC conditions for analyses are given in Table 2.5. This technique was not used for quantification, but only as a tool to determine the progress of certain reactions.

Table 2.5: Important GC settings

Parameter	Setting
Column initial temperature	50°C
Initial hold time	5 min
Heating rate	10°C.min⁻¹
Column final temperature	250°C
Final hold time	10 min
Injector temperature	280°C
Detector temperature	300°C

2.4.2 High Performance Liquid Chromatography

HPLC analyses were carried out on a Hewlett Packard 1100 series with a dual pump system, equipped with a variable UV-visible detector and an autosampler unit. Data were acquired with a Hewlett Packard Vectra personal computer loaded with the HP Chemstation for LC software. All

solvents were HPLC grade and were degassed prior to analysis with a Millipore vacuum degassing unit. Water, adjusted to a pH of 3 (with H_3PO_4), and acetonitrile were used as mobile phases and the instrument was operated in the isocratic mode. A 3.9 x 300 mm Waters μ Bondapak C_{18} (serial no. W90211G041) column or a 4.6 x 250 mm Waters Symmetry Shield RP_8 (serial no. T71701N04) column were used for analyses of reaction samples.

As different substrates were used in the reactions, analysis of the mixtures required different LC conditions. These settings are summarised in Table 2.6. The internal standard method, with nitrobenzene as standard, was used for the analysis of individual components of m-cresol and p-cresol reaction mixtures. Response factors for the compounds of interest were determined by means of a three-level calibration using standard solutions containing known amounts of the analytes and internal standard.

Table 2.6: HPLC parameter settings used for quantitative analysis

Parameter	Setting	
	m-Cresol	p-Cresol
Column	RP₈	C₁₈
Injection volume (μl)	1	1
Mobile phase CH₃CN : H₂O	30 : 70	30 : 70
Flow rate (cm³.min⁻¹)	1	1
UV wavelength (nm)	224	232

2.4.3 Gas Chromatography – Mass Spectrometry

GC-MS analyses was used mainly for qualitative analysis.^{54,55} Use was made of a Hewlett Packard 5890 series II Gas Chromatograph connected to a 5972 series mass selective detector. Separation was achieved with the aid of a 30 m x 0.32 mm i.d.

HP-1 (Chrompack) column. Helium was used as carrier gas, with a flow rate of $1.83 \text{ cm}^3 \cdot \text{min}^{-1}$ and at a column head pressure of $1.15 \text{ kg} \cdot \text{cm}^{-3}$. Data acquisition and manipulation were carried out with HP Enhanced Chemstation software using an Olirite personal computer. Use was made of both on-column and split/ splitless injection modes and using the respective GC syringes (supplied by Hamilton) for each injection mode. Other important chromatographic conditions used are summarised in Table 2.7.

Table 2.7: Chromatographic conditions for GC-MS analysis

Parameter	Setting
Column initial temperature	50°C
Initial hold time	5 min
Heating rate	10°C.min⁻¹
Column final	250°C

temperature	
Final hold time	10 min
Injector temperature^a	280°C
Detector temperature	300°C
Detector solvent delay	2 min

^a – An injector heating program was used with the on-column injection mode.

This mode of operation was mainly used for the identification of specific mass fragments in reaction samples, with the aid of the Chemstation library of organic compounds. The observed fragmentation patterns were then compared to calculated fragmentations.

2.4.4 Nuclear Magnetic Resonance

NMR analysis was carried on a 400 MHz Bruker instrument. Samples were dissolved in CDCl₃ with tetramethylsilane as internal standard. Analyses of data were carried out on a Compaq personal computer with WINNMR software.

2.4.5 Differential Scanning Calorimetry

A Mettler Toledo DSC 820 was used to determine the decomposition temperature of 2,6-dinitro-p-cresol. The sample was placed in an aluminium sample pan (working range up to 400°C) and sealed with a press. Data were analysed on a Mecer premium-X personal computer with the aid of the Mettler STARe software.

2.4.6 UV/ Visible Spectrophotometry

The optimum UV absorbance wavelengths of HPLC standards were first determined with the aid of a Beckman DU[®] 7500 double beam UV/ Vis spectrophotometer with IBM colour screen and Beckman DU series 7000 software. A quartz sample cell (cuvette) was used with methanol or acetonitrile as solvents.

2.4.7 pH determination

Use was made of a Metrohm 654 digital pH meter with a WTW Sentix single glass pH electrode

(serial no. C000304091) to adjust the pH of the aqueous phase (pH = 3) for use in HPLC analysis.

2.4.8 Titrimetric analyses

Nitric acid, of varying concentrations, was standardised by direct titration with borax ($\text{Na}_2\text{B}_4\text{O}_7 \cdot 10\text{H}_2\text{O}$) and using phenolphthalein as acid/ base indicator.

CHAPTER 3

NITRATION OF *m*-CRESOL

3.1 INTRODUCTION

Industrially important nitrocresols have all been prepared by the direct nitration of the cresol in mixtures of concentrated nitric and sulphuric acids or by the nitrosation and subsequent oxidation of the cresol substrate. Highly activated aromatic compounds, such as phenol and cresols, are easily nitrated and may be successfully nitrated even in dilute nitric acid.

The main concern in the nitration of *m*-cresol is the regio-selectivity of the reaction. This is a consequence of the fact that both the hydroxyl and methyl groups are activating para-directors on the aromatic ring. Thus, the substrate is sufficiently activated towards electrophilic attack at any of the available aromatic sites. Of the three nitro-products that are formed in the reaction, only 3-methyl-4-nitrophenol has significant industrial importance. It is possible to separate this isomer from the two ortho-products (3-methyl-2-nitrophenol and 5-methyl-2-nitrophenol)

by steam distillation. However, separation of the two ortho-products is not as easily achieved.

The fourth product in the m-cresol nitration is 2-methyl-1,4-benzoquinone. The formation of this species has been explained in terms of the formation of a phenol radical with the subsequent nucleophilic attack by water to form methylhydroquinone. The methylhydroquinone is then oxidised to the benzoquinone in the nitric acid medium.

Another problem that is often encountered in the nitration of phenolics with nitric acid is that highly activated substrates such as these readily form tarry by-products. The formation of these reaction tars may be the result of the formation of dimers and higher oligomers.

3.2 OBJECTIVES

From the preceding discussion, it is clear that regio-selectivity during the nitration of m-cresol is a major concern. Other points of interest are the minimisation of by-products and tars. The objectives for this section may thus be summarised as follows:

- To investigate the influence of catalysis on the regio-selectivity, conversion, yield and accountability during nitration procedures.
- To evaluate and adjust the levels of reaction parameters such as temperature, acid concentration and acid to substrate ratio by using statistical experimental designs with the view to optimise regio-selectivity, yield and accountability.
- To investigate the effect of alternative nitrating procedures on regio-selectivity.

3.3 RESULTS AND DISCUSSION

3.3.1 Definitions

The following terms were used in the discussion of results:

$$\text{Conversion (\%)} = \frac{(\text{moles of substrate consumed})}{(\text{moles of substrate charged})} \times \frac{100}{1}$$

$$\text{Yield of a product (\%)} = \frac{(\text{moles of specific product formed})}{(\text{moles of substrate charged})} \times \frac{100}{1}$$

$$\text{Selectivity of a product (\%)} = \frac{(\text{moles of a specific product formed})}{(\text{moles of all products formed})} \times \frac{100}{1}$$

$$\text{Accountability (\%)} = \frac{(\text{moles of products and substrate after reaction})}{(\text{moles of substrate charged})} \times \frac{100}{1}$$

Total yield (%) = sum of all product yields

3.3.2 Nitrations using yttrium(III)triflate as catalyst
Waller et al.²⁶ made use of lanthanide triflate salts as catalysts for the nitration of a number of aromatic species in $\text{ClC}_2\text{H}_4\text{Cl}$ with stoichiometric amounts of 65 % HNO_3 . Typically, yields in excess of 95 % were reported for activated aromatic substrates such as toluene and xylene. Apart from the high yields obtained, the use of this catalyst was claimed to offer other advantages too, such as:

- The formation of H₂O as the only by-product;
- The recycling of the catalyst without significant loss in activity; and
- The use of mild reaction conditions which alleviates safety concerns.

In view of the possible advantages of yttrium(III)triflate as nitration catalyst, it was of interest to investigate whether the use of this catalyst would have any influence on the regioselectivity during the nitration of m-cresol with dilute nitric acid solutions. For these reactions, the yttrium(III)triflate was weighed directly into a reaction flask containing 20 cm³ of 1,2-dichloroethane containing m-cresol (0.3249 g; 3 mmol) and nitrobenzene (0.3693 g; 3 mmol). Reactions were carried out with an acid to substrate ratio of 1 : 1. 65 % Nitric acid (0.2879 g; 3 mmol) was added to the mixture over a period of approximately one minute at room temperature. Timing was started as soon as the first drop of acid fell into the reaction flask. The mixture was

placed in a pre-heated oil bath and heated to reflux. Sampling was carried out as described in § 2.3.1.1. HPLC analysis was carried out with the internal standard method as described in § 2.4.2. The reaction was followed for 30 minutes. The results obtained are shown in Table 3.1 and illustrated graphically in Figure 3.1.

Table 3.1: Effect of catalyst concentration on isomer distribution

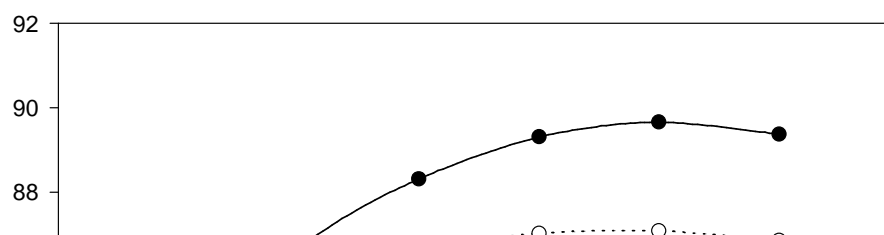
Catalyst amount (mmol)	A : S ^a	Con v. (%)	Yiel d ^b (%)	Accou nt. (%)	Isomer ratio ^c
0.00	1 : 1.001	92.0	88.3	96.3	43.8 : 19.0 : 27.3 : 9.9
0.15	1 : 1.013	96.2	86.9	90.6	44.0 : 19.6 : 27.0 : 9.3
0.30	1 : 1.036	95.0	82.8	87.8	44.0 : 19.7 : 27.0 : 9.3
0.60	1 : 1.005	95.9	83.5	87.6	44.0 : 18.8 : 28.0 : 9.7

^a – Total amount of m-cresol in all reactions (0.3249 g; 3.004 mmol), A = HNO₃ and S = m-cresol

^b – Total yield based on sum of product yields

^c – Isomer distribution: 4-nitro : 2-nitro : 6-nitro : 2-methyl-1,4-benzoquinone

Figure 3.1: Effect of yttrium(III)triflate loading on the



The results presented in Table 3.1 and Figure 3.1 is somewhat surprising in that the presence of $Y(TFA)_3$ (yttrium(III)triflate) clearly had a detrimental effect on the nitration efficiency. There is a significant decrease in both the yield of desired nitration products as well as the accountability of the reaction. Furthermore, the relative amounts of products clearly show that $Y(TFA)_3$ has no influence on the regio-selectivity of the nitration.

These results could possibly be explained in terms of the rapid reaction between nitric acid and m-cresol in the absence of a catalyst under the reaction conditions used. However, the decrease in accountability of the reaction in the presence of $Y(TFA)_3$ cannot be easily explained. In order to understand the role of the catalyst in these reactions, it was decided to investigate the nitration of m-cresol with dilute nitric acid without using a catalyst in more detail.

3.3.3 Nitration with dilute nitric acid

3.3.3.1 General

The nitration of m-cresol in 1,2-dichloroethane with dilute nitric acid was evaluated with the aid of a full 2^3 central composite experimental design with the view to obtaining a thorough understanding of the nitration mechanism and the experimental variables that affect the outcome of the reaction.^{56,57} The optimum points derived from this design are only applicable to the reaction as carried out in the laboratory, and provides no information about process details or possible scaling-up of the reaction.

3.3.3.2 Identification of reaction variables

The optimisation of chemical reactions requires that all experimental variables that may affect the reaction in any way, be identified and investigated.⁵⁸ Such variables would normally include many chemical engineering factors, such as reactor design, heat transfer, feed of materials, etc., for the investigation of production scale processes. However, in this case, chemical engineering factors were excluded from the design since the aim of the experimental design was to determine whether the chosen variables had a significant effect on the design responses on laboratory-scale.

For the present design, the following variables were identified as ones that might impact on the reaction results: the nitric acid concentration, ratio of acid to substrate and the reaction temperature. It was felt that the acid concentration could affect the results because of the change in the amount of aqueous solution introduced into the reaction mixture, and thus also a change in the number of collisions between the aqueous nitronium ions and the substrate molecules in the organic phase. The concentration of the nitric acid also determines the amount of nitronium ions. The acid to substrate ratio is associated with the reaction stoichiometry and hence the degree of substrate conversion and product formation. Reaction temperature was included in the design since temperature plays an important role in the kinetics of individual reactions, both product and by-product formation reactions, and may influence the selectivity of the reaction.

Rate of agitation of reaction mixtures during chemical reactions can have a considerable influence on the reaction kinetics by affecting the frequency of interactions between reactive species. It is desirable that stirring rates should be as high as possible to obtain shorter reaction times, but should under no circumstances be varied between reactions in the design. For that reason, the stirring speed was maintained at 750 rpm for all reactions in the experimental design.

3.3.3.3 Selection of the experimental domain

The experimental variables chosen for the design experiments, as well as the settings for the factor levels, are shown in Table 3.2.

Table 3.2: Factors and factor levels for the experimental design

Code	Factor	Units	Factor Level		
			Low (-)	Centre (0)	High (+)
R	A : S ratio	mmoles	0.8	1.0	1.2
A	Nitric acid conc.	%	40	50	60
T	Temperature	°C	50	60	70

3.3.3.4 Experimental design and responses

Four responses were selected for evaluation in this experimental design. These were conversion, total yield, accountability and yield of 4NMC (3-methyl-4-nitrophenol). The last response, namely yield of 4NMC, was chosen because it gives an indication of the regio-selectivity. The underlying problem in the nitration of m-cresol is that there are four readily formed products, where 4NMC is the most desired product. Thus the manipulation of this response would be the most difficult.

The coded values of the factor levels shown in Table 3.3 were calculated using Equation 3.1.

$$X_i = \frac{u_i - u_o}{\delta_u} \quad \text{Equation 3.1}$$

where x_i = coded value of variable X_i , u_i = natural value of variable X_i at a factorial point, u_o = the natural value of X_i at the design centre, and δ_u = the step size in the natural values of variable X_i .

As the various reagents were weighed out, it was inevitable that small deviations in the theoretical amounts would occur. The actual masses were used in the calculation of the individual ratios as well as the coded levels of the variable settings in the design to minimise experimental error. The experimental values for the coded values in Table 3.3 are given in Table 3.4.

Table 3.3: Full three-factor central composite design

Run no.	Point type	Factor levels		
		R	A	T
1	Factorial	-1	-1	-1
2		1	-1	-1
3		-1	1	-1
4		1	1	-1
5		-1	-1	1
6		1	-1	1
7		-1	1	1
8		1	1	1
9	Star	-1.68	0	0
10		1.68	0	0
11		0	-1.68	0
12		0	1.68	0
13		0	0	-1.68
14		0	0	1.68
15	Centre	0	0	0
16		0	0	0
17		0	0	0
18		0	0	0
19		0	0	0
20		0	0	0

Table 3.4: Design and responses for the nitration of m-cresol

Run no.	Factor levels*			Responses			
	R	A	T	Conv.	Yield	Account.	Yield 4NMC
1	-0.960 (0.808)	-1.060 (39.40)	-0.900 (51)	80.4	77.3	96.9	33.1
2	0.965 (1.193)	-1.060 (39.40)	-1.000 (50)	100.0	86.7	86.7	41.2
3	-1.000 (0.800)	0.974 (59.74)	-1.000 (50)	80.8	76.9	96.1	33.2
4	1.010 (1.202)	0.974 (59.74)	-1.000 (50)	100.0	70.5	70.5	35.0
5	-1.005 (0.799)	-1.060 (39.40)	1.100 (71)	80.0	77.2	97.2	33.3
6	0.990 (1.198)	-1.060 (39.40)	1.000 (70)	99.8	70.5	70.7	34.2
7	-0.935 (0.813)	0.974 (59.74)	1.200 (72)	82.5	78.6	96.1	34.1
8	1.020 (1.204)	0.974 (59.74)	1.100 (71)	99.9	76.3	76.4	35.2
9	-1.660 (0.668)	-0.069 (49.31)	0.1000 (61)	72.2	69.4	97.2	29.8
10	1.665 (1.333)	-0.069 (49.31)	0.100 (61)	99.9	68.9	69.1	24.3
11	-0.035 (0.993)	-1.594 (34.06)	-0.100 (59)	96.3	92.9	96.6	40.0
12	-0.020 (0.996)	1.568 (65.68)	0.000 (60)	96.1	91.4	95.2	39.7
13	-0.030 (0.994)	0.069 (49.31)	-1.800 (42)	93.8	89.7	95.9	38.7
14	-0.065 (0.987)	-0.069 (49.31)	1.600 (76)	99.5	93.4	94.0	41.3
15	-0.035 (0.993)	-0.069 (49.31)	0.000 (60)	100.0	89.7	89.7	40.7
16	-0.005 (0.999)	-0.069 (49.31)	0.000 (60)	99.9	87.6	87.7	40.3
17	-0.065 (0.987)	-0.069 (49.31)	0.000 (60)	99.9	88.9	89.0	40.6
18	0.015 (1.003)	-0.069 (49.31)	0.000 (60)	100.0	89.9	89.9	41.4
19	0.00 (1.000)	-0.069 (49.31)	-0.100 (59)	100.0	88.6	88.6	40.3
20	-0.065 (0.987)	-0.069 (49.31)	0.000 (60)	99.9	88.3	88.4	40.7

*Natural values are given in parenthesis.

3.3.3.5 Statistical evaluation – Analysis of Variance

The second order response surface models were derived using multiple linear least squares techniques (see Appendix 3.1 for details of these calculations) for the conversion of m-cresol, total yield of products, product accountability and yield of 3-methyl-4-nitrophenol (4NMC). These models are given in Equations 3.2, 3.3, 3.4 and 3.5, respectively. In these models, x_1 is the coded value for the ratio of acid to substrate, x_2 is the coded value the concentration of nitric acid, and x_3 the coded value for the reaction temperature.

$$\begin{aligned} \text{Conversion} &= 100.17 + 9.14x_1 + 0.080x_2 + 0.70x_3 - 5.53x_1^2 - && \text{Equation 3.2} \\ &2.00x_2^2 - 1.52x_3^2 - 0.29x_1x_2 - 0.27x_1x_3 - \\ &0.032x_2x_3 \end{aligned}$$

$$\begin{aligned} \text{Total Yield} &= 89.38 - 0.52x_1 - 0.90x_2 - 0.26x_3 - 8.70x_1^2 - && \text{Equation 3.3} \\ &0.73x_2^2 - 0.77x_3^2 - 1.16x_1x_2 - 1.27x_1x_3 + \\ &2.56x_2x_3 \end{aligned}$$

$$\begin{aligned} \text{Accountability} &= 89.22 - 9.61x_1 - 0.99x_2 - 0.94x_3 - 3.11x_1^2 + && \text{Equation 3.4} \\ &1.24x_2^2 + 0.76x_3^2 - 0.87x_1x_2 - 1.00x_1x_3 + \\ &2.53x_2x_3 \end{aligned}$$

$$\begin{aligned} \text{Yield 4NMC} &= 40.77 + 0.16x_1 - 0.23x_2 - 0.020x_3 - 5.04x_1^2 - && \text{Equation 3.5} \\ &0.49x_2^2 - 0.45x_3^2 - 0.41x_1x_2 - 0.78x_1x_3 + \\ &0.61x_2x_3 \end{aligned}$$

The results of the analysis for the individual response surface models are summarised in Tables 3.5 to 3.8 for the conversion of m-cresol, the total yield, the reaction accountability and yield of 4NMC, respectively. (Details of the statistical calculations are summarised in Appendix 3.2.)

Table 3.5: Response surface estimation and ANOVA - Conversion of m-cresol

Factor	Coefficient Estimate	DF	Standard Error	t for H0 Coeff=0	Prob > t
Intercept	100.17	1	0.67		
R	9.14	1	0.45	20.16	< 0.0001
A	0.08	1	0.45	0.18	0.8633
T	0.70	1	0.43	1.61	0.1386
R ²	-5.53	1	0.44	-12.50	< 0.0001
A ²	-2.00	1	0.47	-4.25	0.0017
T ²	-1.52	1	0.41	-3.70	0.0041
RA	-0.29	1	0.58	-0.51	0.6223
RT	-0.27	1	0.57	-0.48	0.6419
AT	0.03	1	0.55	0.06	0.9546
ANOVA					
Source	Sum of Squares	DF	Mean Square	F-Value	Prob > F
Model	1,563.36	9	173.71	64.40	< 0.0001
Residual	26.97	10	2.70		
Lack of Fit	26.96	5	5.39	1800	< 0.0001
Pure Error	0.02	5	0.00		
Cor Total	1,590.33	19			

Table 3.6: Response surface estimation and ANOVA - Total yield

Factor	Coefficient Estimate	DF	Standard Error	t for H0 Coeff=0	Prob > t
Intercept	89.38	1	2.00		
R	-0.52	1	1.36	-0.38	0.7107
A	-0.90	1	1.36	-0.66	0.5241
T	-0.26	1	1.30	-0.20	0.8479
R ²	-8.70	1	1.33	-6.55	< 0.0001
A ²	-0.73	1	1.41	-0.51	0.6190
T ²	-0.77	1	1.23	-0.62	0.5476
RA	-1.16	1	1.74	-0.67	0.5203
RT	-1.27	1	1.71	-0.75	0.4728
AT	2.56	1	1.65	1.55	0.1516
ANOVA					

Source	Sum of Squares	DF	Mean Square	F-Value	Prob > F
Model	1,169.70	9	129.97	5.35	0.0075
Residual	243.05	10	24.31		
Lack of Fit	239.30	5	47.86	63.76	0.0002
Pure Error	3.75	5	0.75		
Cor Total	1,412.75	19			

Table 3.7: Response surface estimation and ANOVA - Accountability

Factor	Coefficient Estimate	DF	Standard Error	t for H0 Coeff=0	Prob > t
Intercept	89.22	1	1.63		
R	-9.61	1	1.11	-8.67	< 0.0001
A	-0.99	1	1.11	-0.90	0.3910
T	-0.94	1	1.06	-0.89	0.3950
R ²	-3.11	1	1.08	-2.88	0.0164
A ²	1.24	1	1.15	1.07	0.3086
T ²	0.76	1	1.01	0.75	0.4700
RA	-0.87	1	1.42	-0.61	0.5541
RT	-1.00	1	1.39	-0.72	0.4889
AT	2.53	1	1.34	1.88	0.0892

ANOVA					
Source	Sum of Squares	DF	Mean Square	F-Value	Prob > F
Model	1,542.58	9	171.40	10.62	0.0005
Residual	161.37	10	16.14		
Lack of Fit	157.94	5	31.59	46.07	0.0003
Pure Error	3.43	5	0.69		
Cor Total	1,703.95	19			

Table 3.8: Response surface estimation and ANOVA - Yield 4NMC

Factor	Coefficient Estimate	DF	Standard Error	t for H0 Coeff=0	Prob > t
Intercept	40.77	1	0.82		
R	0.16	1	0.56	0.29	0.7745
A	-0.23	1	0.56	-0.42	0.6856
T	-0.02	1	0.53	-0.04	0.9703
R ²	-5.04	1	0.54	-9.26	< 0.0001
A ²	-0.49	1	0.58	-0.85	0.4131

T ²	-0.45	1	0.51	-0.89	0.3943
RA	-0.41	1	0.71	-0.57	0.5810
RT	-0.78	1	0.70	-1.12	0.2890
AT	0.61	1	0.68	0.90	0.3909
ANOVA					
Source	Sum of Squares	DF	Mean Square	F-Value	Prob > F
Model	364.66	9	40.52	9.94	0.0006
Residual	40.78	10	4.08		
Lack of Fit	39.96	5	7.99	49.13	0.0003
Pure Error	8.13E-01	5	0.16		
Cor Total	405.43	19			

Several aspects regarding the results summarised in Tables 3.4 to 3.8 deserve further comment.

- Substrate (m-cresol) conversion varies between 72 mole % and 100 mole % and appears to be a direct function of the amount of nitric acid used in a particular reaction. There is an excellent correlation between the amount of nitric acid charged and the amount of m-cresol converted indicating that the reaction between nitric acid and m-cresol occurs in a 1 : 1 ratio.
- The total yield of reaction products varies between 69 mole % and 97 mole % and is consistently lower than the conversion of m-cresol achieved. This is a clear indication of the formation of undesirable side products.
- As a result of the formation of undesirable side products suggested above, the accountability of the reaction in terms of the products quantified is never 100 %.
- The yield of 4NMC varies between 24 % and 41 %, indicating that the manipulation of regio-selectivity during the nitration reaction is possible to some extent.
- The statistical evaluation of the effects of the individual reaction variables on the experimental responses shows that the acid : substrate ratio has by far the largest influence, being significant for the conversion, total yield, accountability and yield of 4NMC.
- Other variables that show significant influences on one or more responses include reaction temperature (conversion), acid concentration (conversion),

and the two-factor interaction effect between acid concentration and reaction temperature (yield and accountability).

- The analysis of variance for all four of the derived response surface models shows that the models adequately describe the individual response surfaces (as shown by the low P -values for the model in the individual ANOVA-Tables), but the individual responses predicted by these response surface models show significant lack-of-fit (as shown by the low P -values for lack-of-fit). This behaviour in the individual response surfaces is quite uncommon and to obtain further information on the behaviour of the response surface models, analyses of the residuals (the differences between actual and predicted responses) were made. These analyses are illustrated graphically in Figures 3.2 – 3.9.

Figure 3.2: Normal probability plot of residuals - conversion

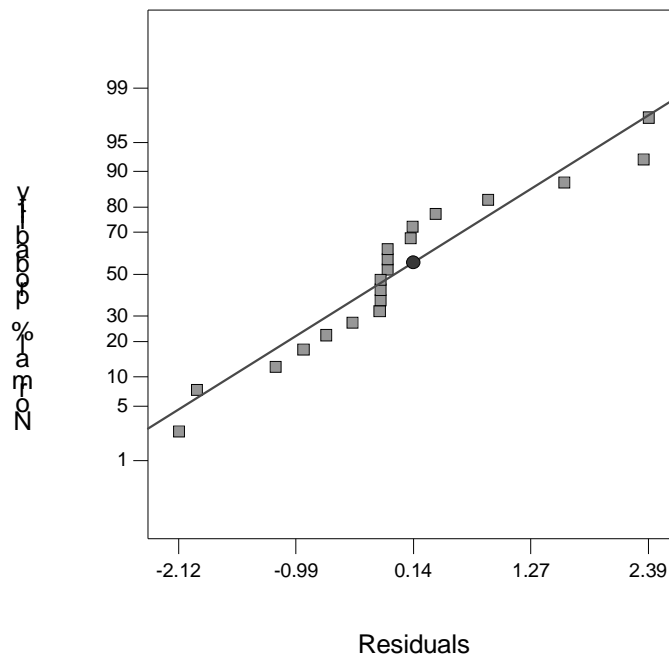


Figure 3.3: Residuals vs. predicted response – conversion



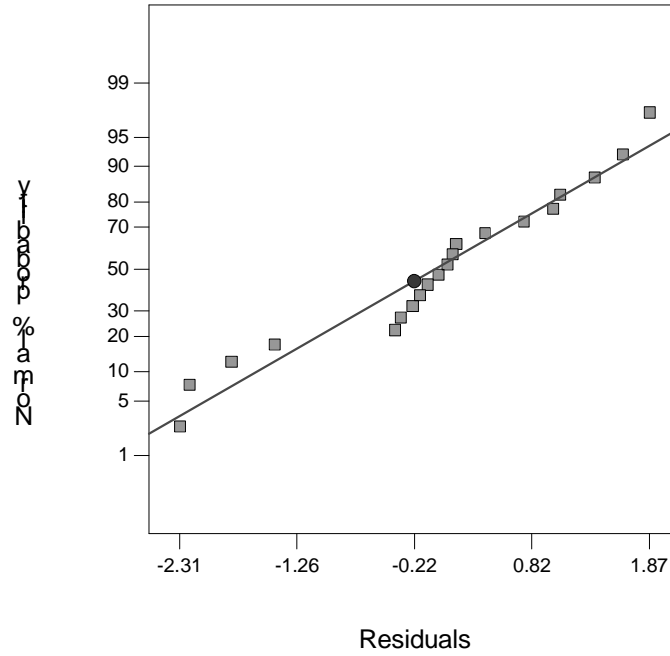
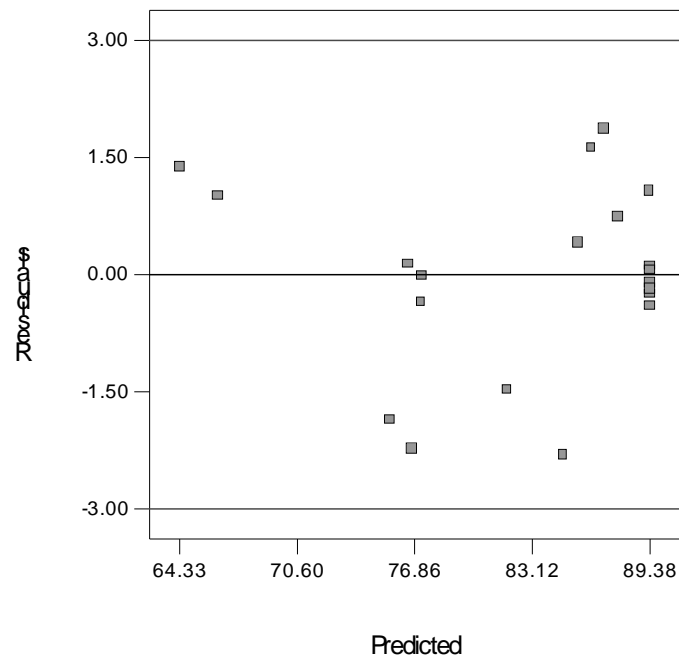
Figure 3.4: Normal probability plot of residuals – total yield**Figure 3.5: Residuals vs. predicted response – total yield**

Figure 3.6: Normal probability plot of residuals - accountability

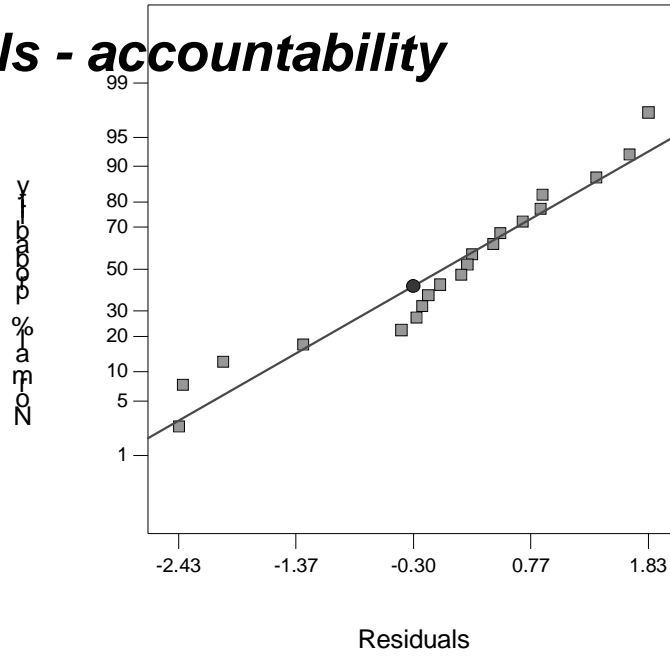


Figure 3.7: Residuals vs. predicted response - accountability

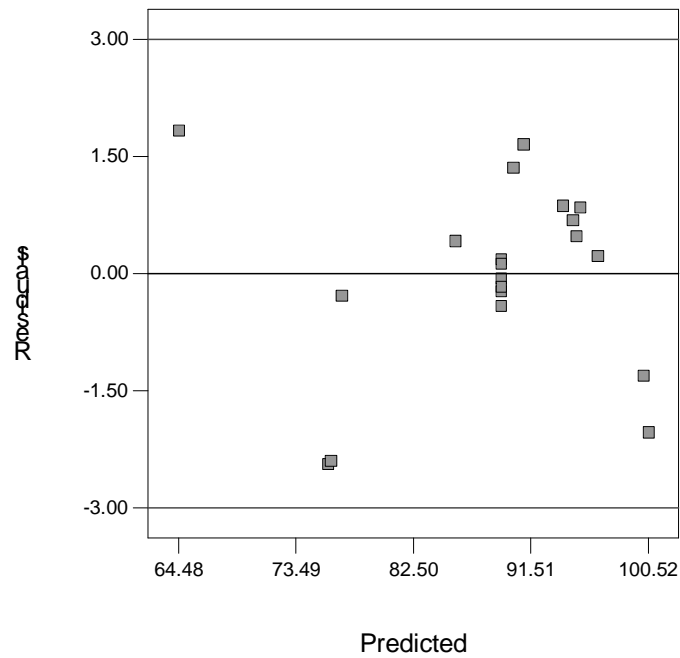
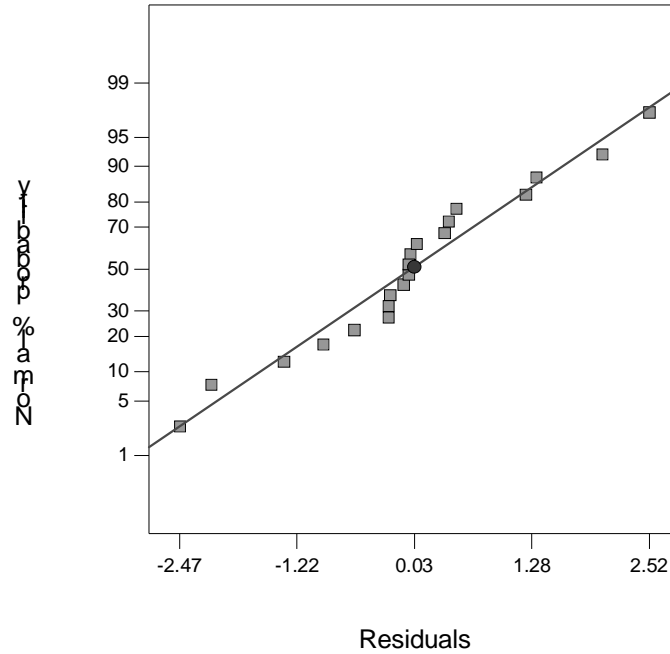
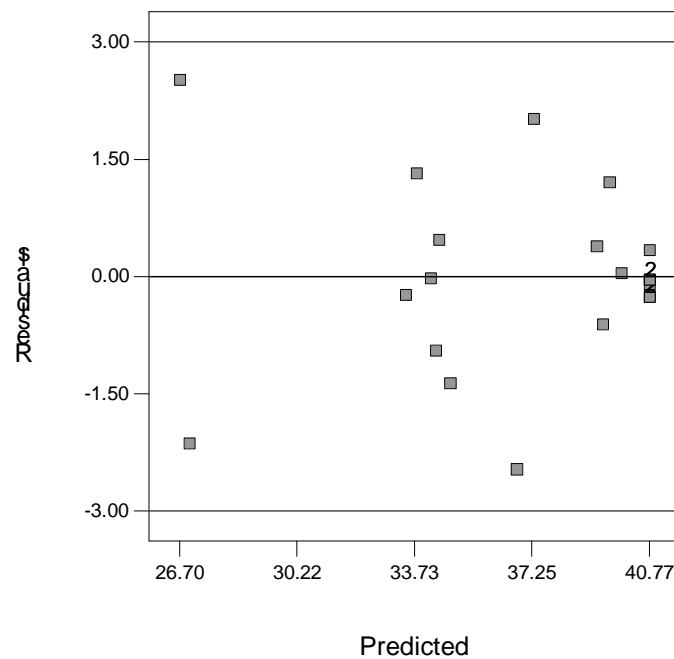


Figure 3.8: Normal probability plot of residuals – yield of 4NMC**Figure 3.9: Residuals vs. predicted response – yield of 4NMC**

Two types of analyses^{59,60} were carried out, namely normal probability plots of the residuals, and plots of the residuals versus the individual predicted responses. In the first case, because the residuals represent the experimental error in each experimental point and because experimental error should always be distributed normally, straight lines are expected with the individual residuals falling on or nearly on these straight lines. From the individual plots (Figures 3.2, 3.4, 3.6 and 3.8) it can be seen that there appears to be some or other cyclic deviation about the straight line, but the overall trend is linear. In the case of the plots of the residuals versus predicted response, a random distribution of points about the zero-line is expected with the outer bands remaining parallel to the zero line. There does not appear to be any abnormality in the plots (Figures 3.3, 3.5, 3.7 and 3.9) obtained. Both these analyses confirms the results of the ANOVA i.e. the models describe the response surfaces adequately, but with poor prediction power.

The reason for the observed results may possibly be traced to the manner in which the nitration reactions were performed. It should firstly be noted that the experimental variation at the six centre points, as indicated by the relative value of the mean square for "Pure Error" in the respective ANOVA-Tables, is remarkably small. This clearly indicates that both the synthetic procedure and the analytical method give reliable results. Secondly, the variation in the experimental error in the factorial and star points of the design is, however, comparatively large as is indicated by the mean square values for "Lack-of-fit" in the respective ANOVA-Tables. This suggests that either the synthetic method, or the analytical method, or both, is not reliable. Since the analytical method remained exactly constant and because the centre points were performed randomly between the design points, the possibility of the analytical method being unreliable may be ignored. Hence remaining is the synthetic method, which is not constant between the design points and the centre points. The reason for this is the inclusion of "acid : substrate ratio" and "acid concentration" as variables in the design without correcting for the total volume of the final reaction mixture. In the centre points, there would be no variation in the total reaction volume, but in the design points, the total reaction volume would vary

symmetrically above and below the total volume at the centre points. The effect of this cyclic variation was clearly noted in the normal probability plots of the residuals described previously.

3.3.3.6 Analysis of the fitted response surfaces

Although the individual response surface models cannot be used for the prediction of expected results at specific settings of the reaction variables due to a poor lack-of-fit, they may still be used to analyse the trends that will be observed when varying the reaction variables in the design space. For the purpose of this investigation, this was considered adequate in view of the initial objective of this investigation, namely to find the relationship between individual reaction variables and the reaction outcome (conversion, yield and regio-selectivity). These trends are best illustrated with the aid of contour diagrams of the individual response surfaces as shown in Figures 3.10 – 3.13.

The contour diagrams shown in Figures 3.10 – 3.13 were constructed by keeping one of the three variables constant at its centre point value whilst varying the other variables between the design limits. The following aspects concerning these plots deserve some comment.

- The contour diagrams for the substrate conversion (Fig. 3.10) show that acid concentration and reaction temperature have virtually no influence on the level of substrate conversion, and that maximum conversion is obtained with high acid to substrate ratios.
- The diagrams for total yield (Fig. 3.11) shows that the acid : substrate ratio has again the largest effect on the yield response with the best responses being obtained at acid : substrate ratios approaching 1 : 1. In this case,

however, there appears to be a small, yet significant, increase in the total yield with decreasing acid concentration.

- As in the case of total yield, the acid : substrate ratio again exerts the largest influence on the accountability of the reaction, but now increased accountability is observed with decreasing acid : substrate ratios (Fig. 3.12).

Figure 3.10: Contour diagrams for conversion of m-cresol

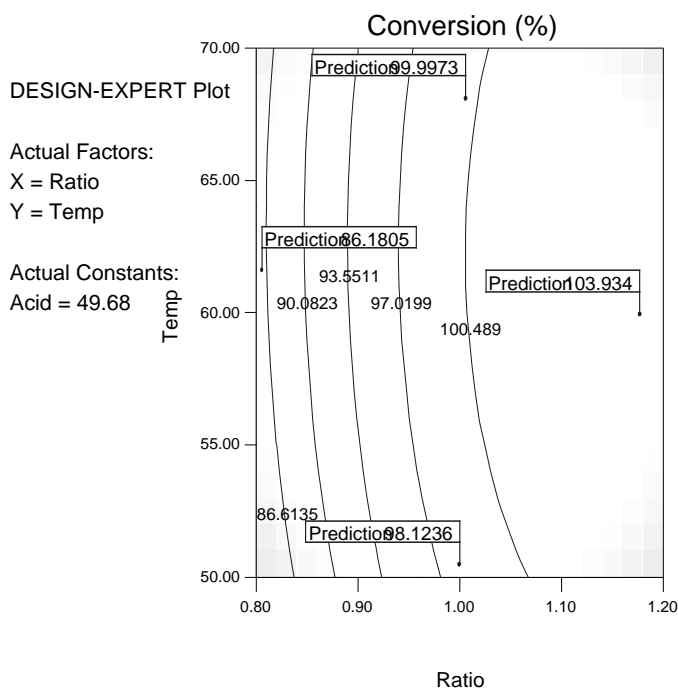
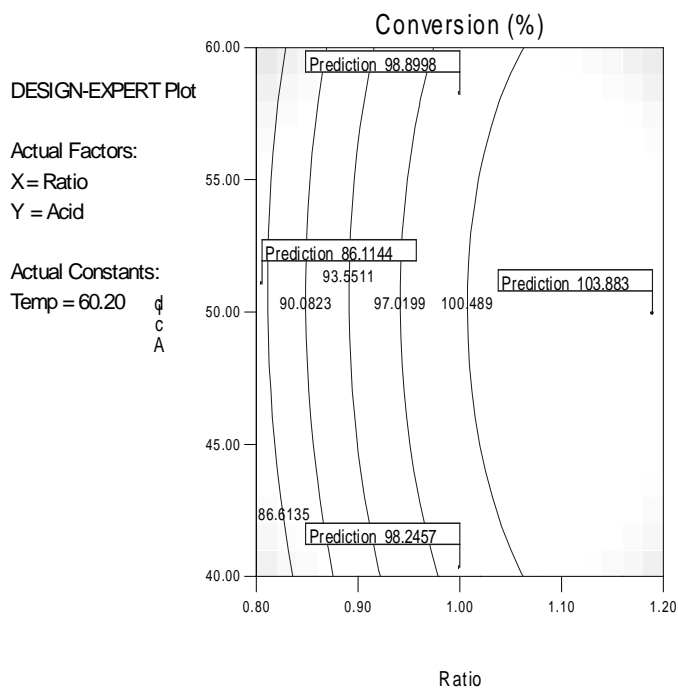


Figure 3.11: Contour diagrams for total yield

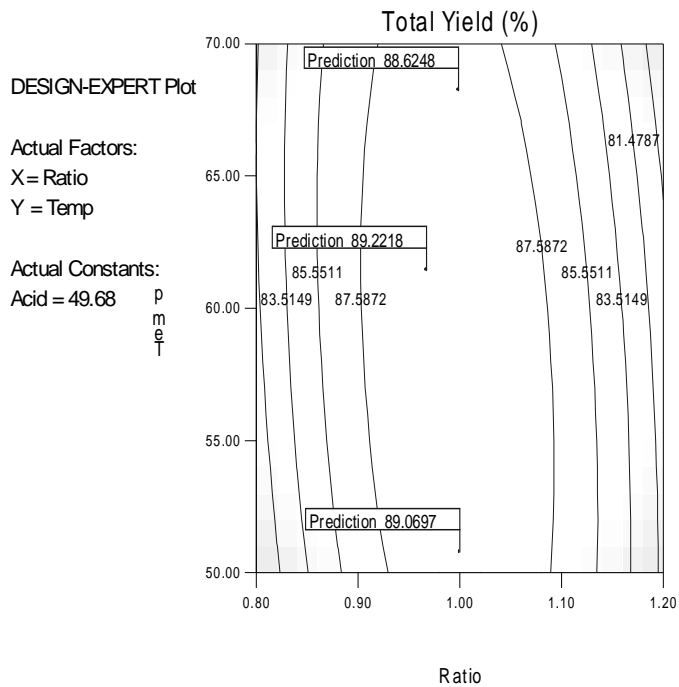
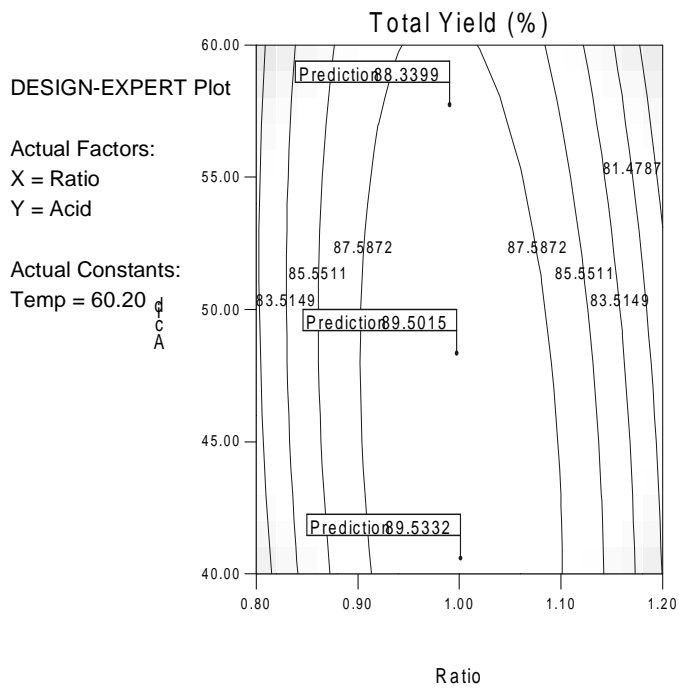


Figure 3.12: Contour diagrams for product accountability

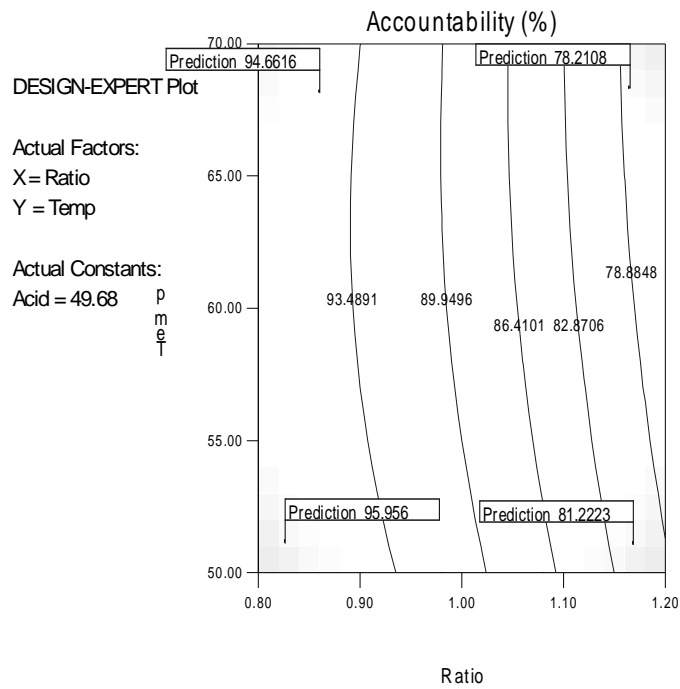
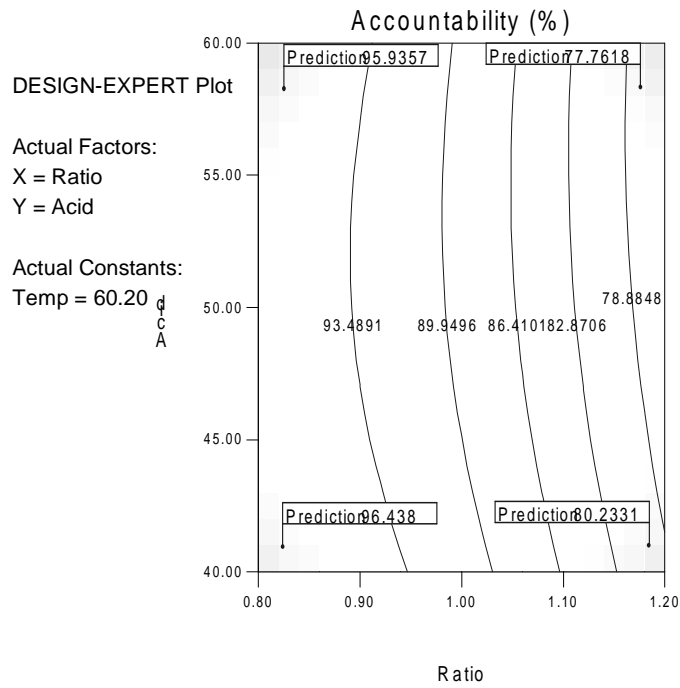
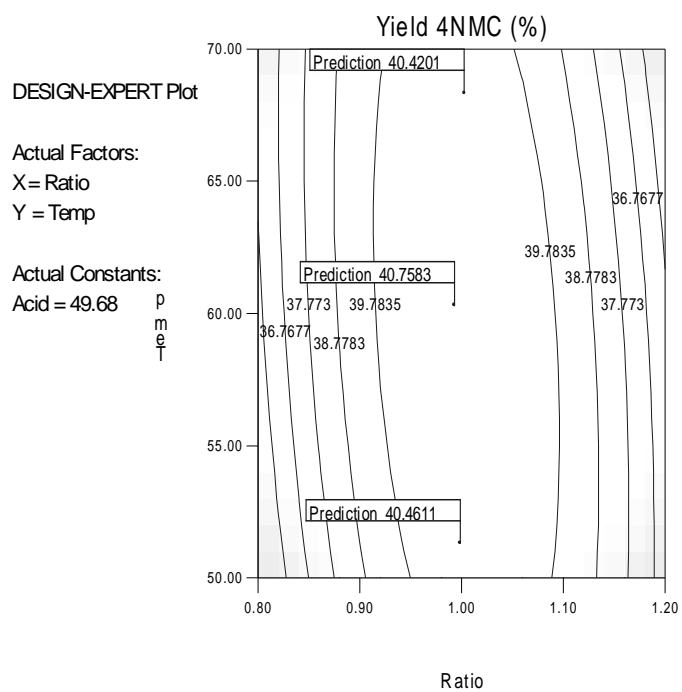
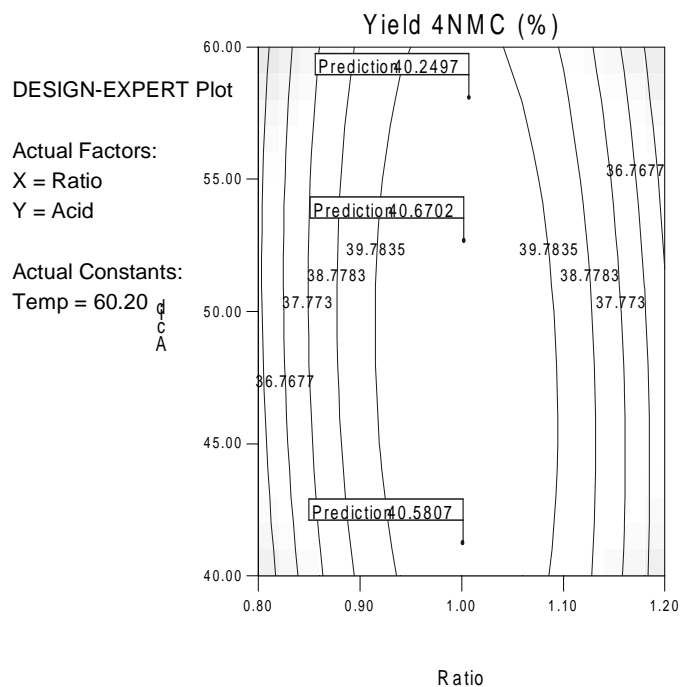


Figure 3.13: Contour diagrams for yield of 4NMC



- **At acid : substrate ratios approaching 1 : 1, both decreasing acid concentration and decreasing reaction temperature improves the accountability in terms of the four reaction products quantified.**
- The diagrams for 4NMC yield (Fig. 3.13) again show that improved selectivities are obtained with acid : substrate ratios approaching 1 : 1, with decreasing acid concentration having only a small positive effect on the selectivity.

3.3.3.7 Confirmatory experiments

From the discussions in the preceding section, the following strategies can be proposed to increase the responses for total yield, accountability and yield of 4NMC:

- Keep the acid : substrate ratio as close to 1 : 1 as possible.
- Decrease the acid concentration as far as is practically possible.
- Decrease the reaction temperature.

Several experiments were carried out in order to test the validity of the above proposals. These reactions were carried out using the same method as described for the initial design. The results from these experiments are summarised in Table 3.9.

Table 3.9: Validity of design

Temp. ^a (°C)	Acid ^b (%)	A : S	Conv. (%)	Yield (%)	Account. (%)	Isomer ratio ^c
0	39.4	1 : 1.007	72.8	69.6	96.8	42.0 : 19.3 : 26.0 : 11.4
5	39.4	1 : 1.001	76.7	73.9	97.2	42.5 : 20.5 : 25.7 : 11.7
10	39.4	1 : 0.999	75.6	72.2	96.6	40.9 ; 20.8 : 26.0 : 10.8

Results after 30 min reaction time

^a – Bath temperature

^b – Acid concentration - % m/m

^c – Isomer distribution: 4-nitro : 2-nitro : 6-nitro : 2-methyl-1,4-benzoquinone

The results shown in Table 3.9 indicate that the proposals made above do indeed hold. The combination of a lower acid concentration and lower temperature results in a significantly improved accountability for the reaction, albeit at lower conversions. The yield of 4NMC is also slightly improved, but the improvement is too small to warrant further manipulation. In fact, decreasing the acid concentration to below ca. 35% results in very slow reactions (less than 10% substrate conversion after three hours). A limit of the nitric acid concentration seems to exist, below

which it ceases to be possible to bring about successful nitration at such low temperatures, whether the reaction is catalysed or not. However, the limit seems to be lowered when the reaction is catalysed by yttrium(III)triflate. This effect is illustrated in Table 3.10.

Table 3.10: Lack of nitration with low acid concentrations at low temperature

Acid ^a (%)	Y(TFA) ₃ ^b (mol %)	A:S	Rxn time (min)	Conv. (%)	Yield (%)	Account. (%)
10	10	1 : 0.992	180	-	-	101
20	10	1 : 1.006	60	19.8	0.1	80.4
34	0	1 : 1.014	20	-	-	102

^a – Acid concentration - % m/m

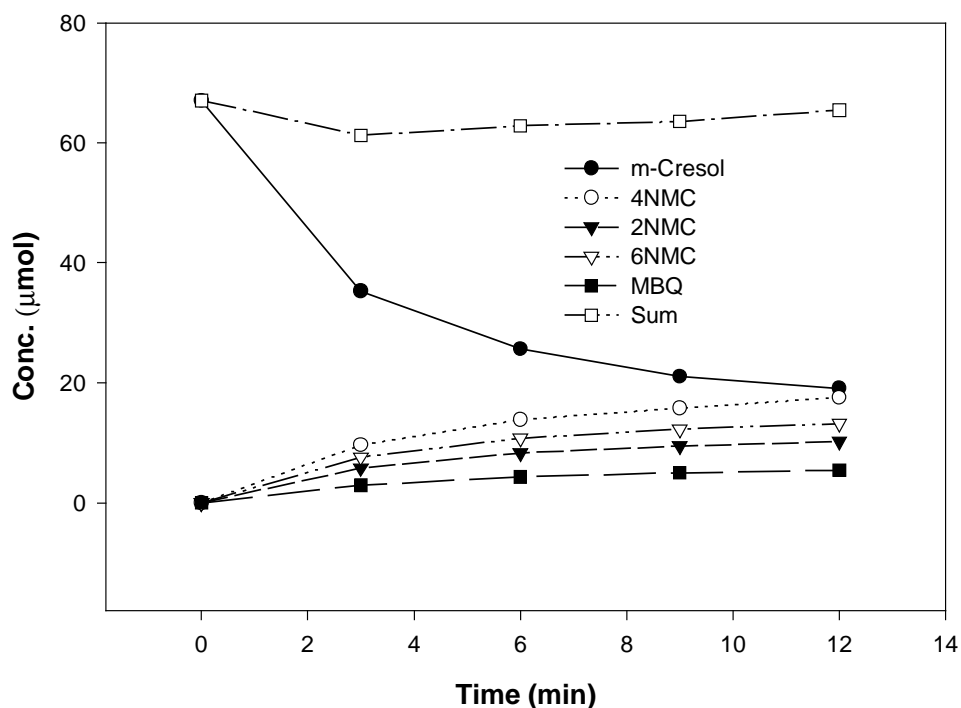
^b – Yttrium(III)triflate - mol % of substrate

All reactions – 3 mmol substrate in 20.00 cm³ 1,2-dichloroethane; 0 °C

In another experiment, a product distribution diagram was constructed for the nitration of m-cresol. In this case, the reaction was carried out with 40 % nitric acid at 0°C without any added catalyst (yttrium triflate). This was done so that the reaction may be sufficiently slow so as to be able to construct a reasonable reaction profile. The aim of this experiment was to establish whether any of the m-cresol nitration products formed at a higher rate than the other products. It would serve as an indication of the viability of kinetic control of the regio-selectivity, i.e. the case where the formation of one product occurs quicker than the others; if this is the required product, reaction times will be shortened, thus not allowing the unwanted products to form.

An A : S of 1 : 1 was maintained with the addition of 3 mmol m-cresol (0.3244 g) and internal standard (nitrobenzene; 0.3693 g) into 20.00 cm³ 1,2-dichloroethane. Aliquots (0.5 cm³) were taken at three minute intervals and were immediately quenched by addition to 5 cm³ water, in order to dilute the nitric acid to such an extent that no further nitration would take place. The organic layer was separated and further diluted with 2.00 cm³ acetonitrile. Analyses of samples were carried out using HPLC, as described in § 2.4.2. The product distribution diagram is given in Figure 3.14.

Figure 3.14: Product distribution diagram for the nitration of m-cresol at 0°C with 40 % nitric acid



MBQ – 2-methyl-1,4-benzoquinone

The product distribution curve clearly shows that all the products form at approximately the same rate. It also seems that the relative ratios of the different products with respect to each other are maintained throughout the reaction. The reaction conditions under which this reaction was carried out (low temperature, no catalyst and low acid concentration) was too mild to force the reaction to completion as only approximately 70 % of the substrate was converted. The accountability of the reaction (indicated on the graph as “sum”) initially dipped but soon increased until it practically remained constant for the remainder of the reaction. This dip could be caused by the initial formation of an intermediate that may not be quantified, but which then reacts further to form a nitrocresol product, and thus ultimately added into the material balance.

3.3.4 Nitrations using yttrium(III)triflate at low temperatures

In view of the results obtained above, it is clear that more effective nitration results can be achieved at low acid concentrations and low nitration temperatures. However, there appears to be a limit in how far the reaction temperature and the acid concentration can be reduced whilst still maintaining practical reaction rates. It was therefore decided to investigate the use of yttrium(III)triflate as catalyst under these conditions, not only to establish whether the use of the catalyst will enable the use of reaction conditions not practically feasible in the absence

thereof, but also to establish whether the catalyst may display any regio-selective preference. In the studies described previously (§ 3.3.2), it was concluded that the effect of the catalyst was masked by the “extreme” reaction conditions (high temperatures and acid concentration) so that the effect of the catalyst could not be seen. In order to establish whether there is indeed a catalytic effect, several reactions were carried out at reduced acid concentrations and low nitration temperatures using yttrium(III)triflate as catalyst. The results of these studies are summarised in Table 3.11.

Table 3.11: Nitration with yttrium(III)triflate at low acid concentrations and low temperatures

Acid ^a (%)	A:S	Conv. (%)	Yield ^b (%)	Account. (%)	Isomer ratio ^c
34 ^d	1 : 1.014	95.6	94.2	98.6	40.8 : 19.1 : 27.1 : 11.1
34 ^e	1 : 0.992	99.9	84.8	85.0	41.2 : 17.6 : 28.3 : 12.9
40 ^d	1 : 1.004	95.1	91.0	95.9	42.3 : 20.3 : 26.1 : 11.2

^a – Acid concentration: % m/m

^b – Total yield = sum of product yields

^c – Order of isomers: 4-nitro; 2-nitro; 6-nitro; 2-methyl-1,4-benzoquinone

All reactions carried out at 0°C; 30 min total reaction time; catalyst load of 10 mol% relative to the substrate

^d – Substrate load of 1.6 % (m/v)

^e – Substrate load of 4.8 % (m/v)

It is clear from the above results that the Y(TFA)₃ catalyst does in fact facilitate the reaction, since there is almost full conversion after only 30 minutes reaction time. When nitration was carried out in the absence of added triflate under the same conditions (0°C and 40 % nitric acid; Table 3.9), only approximately 70 mole % of the substrate was converted. Since conversion is practically complete in this case, the total yield is also much higher. Accountability is comparable with those obtained previously (Table 3.9). In the

second reaction, a higher substrate loading was used, which had a clear detrimental effect on the yield and accountability. It seems that by increasing the substrate loading, one is also increasing the relative number of side reactions. Although there is very little difference in the product selectivities, it does seem that the reaction with the highest acid concentration also produced the highest selectivity to 4NMC, but at a lower accountability. It is thus clear that the addition of yttrium(III)triflate does promote the nitration reaction, but that this catalytic effect is masked under harsher reaction conditions. Addition of the catalyst hence also broadens the range of conditions under which the nitration reaction may be successfully carried out, although there seems to be no need to add it when the reaction is carried out with relatively concentrated nitric acid (higher than 40 %) and at temperatures above zero.

3.3.5 Nitration using clays

Several nitration procedures for the nitration of m-cresol have been reported in the literature where regio-selectivities were found to be different from the expected statistical distribution. These procedures include the use of solid catalyst supports such as montmorillonite K10.²³⁻²⁵ The fact that these reactions were carried out in very mild conditions, using relatively inexpensive reagents, also added to the allure of using clays. Two methods, using respectively “Claycop” and “Clayfen”, showed promise in modifying the isomer distribution during nitrations of m-cresol. “Clayfen”, for example, was reported by Cornelius and Laszlo^{23,24} to result in improved selectivities towards para-nitration. “Claycop”,²⁵ on the other hand, was reported to increase the selectivity towards ortho-nitration. In view of these reports, several experiments were carried out using these reagents to establish whether any significant deviations in the regio-selectivity of the nitration do in fact occur and, if so, whether further manipulation of these procedures were possible to make these nitrations practically more attractive.

3.3.5.1 “Claycop”

“Claycop” was prepared as reported by Grigante et al.²⁵ and outlined in Chapter 2 (§ 2.3.1.4). The m-cresol and internal standard was weighed into a reaction flask (10 mmol of each) and mixed with carbon tetrachloride (30 cm³). To this was added Claycop (2.4 g) and acetic anhydride (7.5 cm³). Typical results obtained for the “claycop” nitration are given in Table 3.12. Other reaction conditions were as follows:

stirring rate – 750 rpm
temperature - ambient
reaction time - 1 hour

Table 3.12: Nitration of *m*-cresol with “claycop”

	This Work	Grigante Et al.²⁵
Conversion (%)	21.9	Nr ^a
Yield (%)	19.1	90
Accountability (%)	97.2	Nr ^a
Selectivity 4NMC (%)	37.7	15
Selectivity 2NMC (%)	21.5	55
Selectivity 6NMC (%)	30.4	Nr ^a
Selectivity 2-methyl-1,4-benzoquinone	10.5	Nr ^a

^a – Not reported

As can be seen from the above results, we were not able to reproduce the results obtained by Grigante et al.²⁵ In fact, the yield and conversion was very low in comparison to that previously reported. In addition, the selectivities to the individual components were also found to be of a different order to that reported, with 4NMC again being the major component. A careful analysis of the data presented in Table 3.12 shows that the sum of the 2- and 6-isomers appears to be very close to the value reported for 2NMC by the authors. It therefore seems likely that the analytical technique used by these authors was not capable of distinguishing between 2NMC and 6NMC, nor capable of determining the concentration of the 2-methyl-1,4-benzoquinone. In view of the results obtained in our laboratories, there seems to be no advantage of further considering the use of “claycop” reagents for these nitrations, especially since additional steps are required in that these reagents need to be prepared and relatively long reaction times required.

3.3.5.2 “Clayfen”

Clay-supported ferric nitrate was prepared by mixing ferric nitrate nonahydrate with K10 clay in acetone, as described in § 2.3.1.3.^{23,24} The m-cresol and internal standard was weighed into a reaction flask (10 mmol of each) and diluted with diethyl ether (50 cm³). “Clayfen” was weighed into the flask (5 g). Typical results for the “clayfen” nitration are given in Table 3.13. Other reaction conditions were as follows:

stirring rate – 750 rpm

temperature - ambient

reaction time – 1 hour

Table 3.13: Nitration of m-cresol with “clayfen”

	This Work	Laszlo et al.^{23,24}
Conversion (%)	56.0	nr ^a
Yield (%)	54.8	nr ^a
Accountability (%)	99.1	nr ^a
Selectivity 4NMC (%)	41.4	34
Selectivity 2NMC (%)	22.6	20
Selectivity 6NMC (%)	26.8	nr ^a
Selectivity 2-methyl-1,4-benzoquinone (%)	8.9	nr ^a

^a – Not reported

The results from these experiments were slightly better than for “claycop”. The conversion was, however, relatively low, taking into account that the reaction was left for 1 hour. The total yield obtained in this reaction is very close to the 58% claimed for the nitration of p-cresol. As can be seen, the accountability of products was very high, although the selectivity to 4NMC was higher than the

34% claimed by the authors. As in the case of “claycop”, no mention was made of the formation of the other reaction products.

3.3.6 Nitration with nitric and sulphuric acid mixtures

The use of mixtures of nitric and sulphuric acid in nitrations has been practiced for as long as the technique has been known. The sulphuric acid ionises the nitric acid into free nitronium ions, which are the real attacking electrophile. In addition to sulphuric acid, these reactions (nitrations) have also been carried out successfully by mixing nitric acid with a variety of strong acids such as trifluoroacetic acid and trifluoromethanesulphonic acid.^{30,31} In a series of publications by Coombes and his fellow workers,^{32,33} it was shown that the concentration of sulphuric acid could influence the regio-selectivity in the nitration of “activated” aromatic substrates such as methylanisole and m-cresol. For m-cresol, this apparent decrease in the ortho/ para ratio was observed over the range of sulphuric acid concentrations of 58 – 81 %. The proportion of para-products is claimed to have changed from 33 to 52 % over this concentration range. Another interesting point about the work carried out by this group was the fact that the formation of 2-methyl-1,4-benzoquinone was not reported.

On the other hand, nitrations in highly concentrated acid mixtures have some inherent drawbacks, such as the fact that tars and other side products are often formed, not to mention the formation of large amounts of acid wastes. The possible increase in para-selectivity does offer possible advantages, provided that the disadvantages referred to above can be alleviated.

For these reactions, m-cresol (0.3244 g; 3 mmol) was weighed into a reaction flask and mixed with 20 cm³ 1,2-dichloroethane. Sulphuric acid (98 %) was added in a 2 : 1 ratio with 65% nitric acid (0.28 g). The ratio of nitric acid to m-cresol was set at 1 : 1. The reaction was carried out at room temperature whilst

stirring at 750 rpm. The mixture was left to react for one hour. Results obtained are summarised in Table 3.14.

Table 3.14: Nitration of *m*-cresol with a mixed acid system

Conversion (%)	98.0
Yield (%)	51.2
Accountability (%)	53.1
Yield 4NMC (%)	25.0
Isomer ratio ^a	48.8 : 20.3 : 29.3 : 1.5

^a – order of isomers: 4NMC : 2NMC : 6NMC : 2-methyl-1,4-benzoquinone

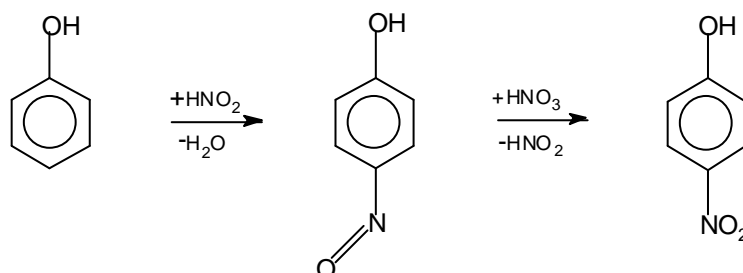
The first interesting point to raise about the results obtained for the nitration of *m*-cresol with the mixed acid system is that the amount of 2-methyl-1,4-benzoquinone formed is considerably reduced in comparison with nitration systems investigated earlier in this work. Secondly, the selectivities to 4NMC (approx. 49 %) are considerably higher than that observed for previous systems. It is, however, of interest to note that the selectivities to 2NMC and 6NMC remain virtually unchanged so that it appears that the increased selectivity to 4NMC was brought about at the direct expense of the selectivity to 2-methyl-1,4-benzoquinone. The last point of interest concerning these results is the rather poor overall yield and accountability. The formation of tarry by-products could be visually established. The reaction mixture in this case was a dark, thick, syrupy liquid, far removed from the deep orange to red mixtures obtained previously.

3.3.7 Proposed mechanism for the formation of 2-methyl-*p*-benzoquinone

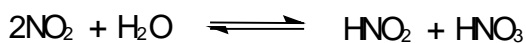
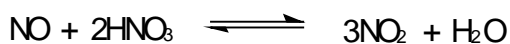
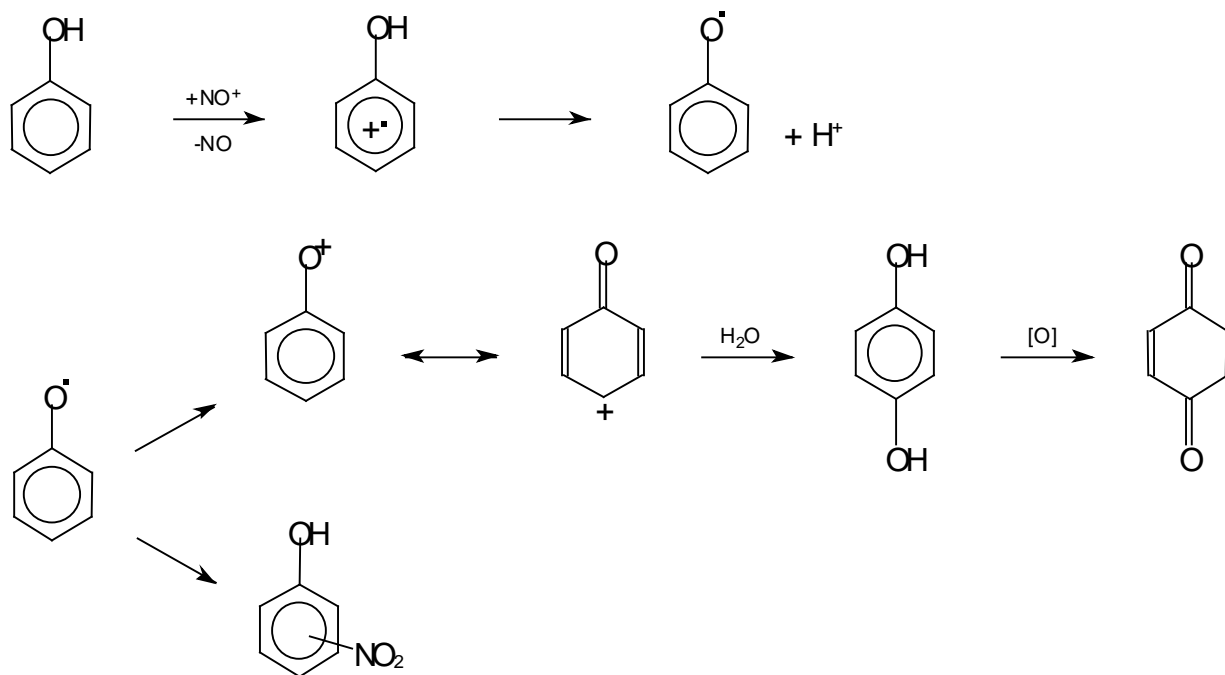
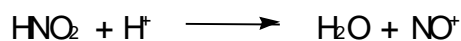
The nitration of phenolic compounds is a very old reaction, being described for the first time in 1875. Despite the importance of nitrophenols for industry, being used as intermediates in the production of dyes, pharmaceuticals and agrochemicals, only Rhône Poulenc carries out this reaction on large industrial scale. Nitration of phenolic compounds is known to be “messy” and despite a number of specific studies, the exact mechanism is still not very clear.

Two mechanisms⁶¹ are currently being accepted to occur simultaneously during the nitration of phenolic compounds, namely nitrosation of the aromatic ring followed by oxidation of the initially formed nitrosophenol compound (Scheme 3.1), and the nitration of the aromatic ring catalysed by nitrous acid (Scheme 3.2).

Scheme 3.1: Nitrosation



Scheme 3.2: Nitration

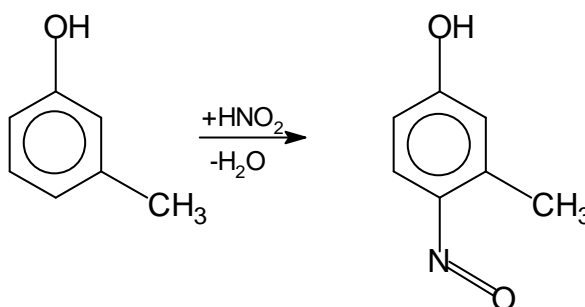


The formation of 2-methylbenzoquinone, during the nitration of m-cresol in yields of around 10 mole %, has been explained in terms of the oxidation of the phenoxy radical to the phenoxonium cation which reacts with water to give the hydroquinone, and subsequent oxidation of the hydroquinone to the benzoquinone. However, two equivalents of nitric acid are required for the oxidation of the hydroquinone, implying that an excess of nitric acid will be required for full conversions during the nitration reaction of m-cresol when 2-methylbenzoquinone is formed. In all the reactions where a 1 : 1 nitric acid : m-cresol ratio has been used, full or near quantitative conversions have been obtained, despite the formation of 2-methylbenzoquinone in yields exceeding 10 mole %.

These findings in our laboratories hence implied a different mechanism at work to that proposed for the formation of the benzoquinone. The actual operative mechanism requires the use of only one equivalent of nitric acid in order to transform m-cresol into 2-methylbenzoquinone, not two, according to our findings.

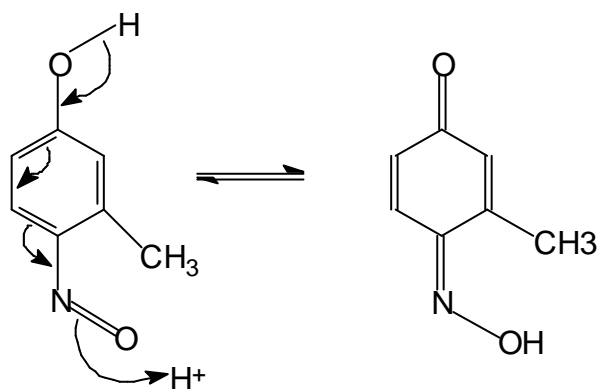
We therefore propose the following in which m-cresol is initially nitrosated according to the reported mechanism (Scheme 3.3:)

Scheme 3.3: Initial nitrosation

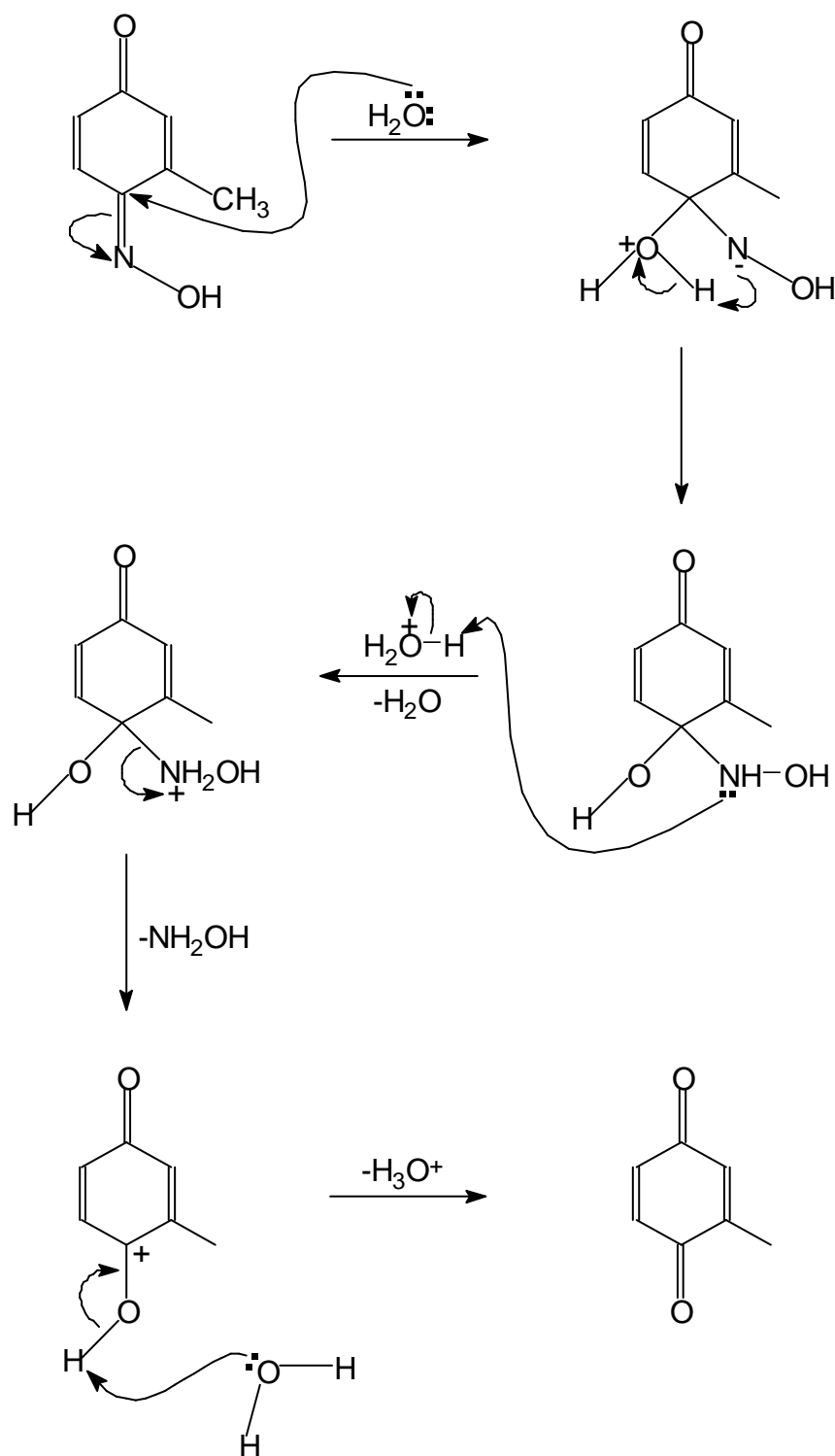


The 3-methyl-4-nitrosophenol so formed is merely a tautomeric form for the corresponding 3-methyl-p-benzoquinone monoxime (Scheme 3.4).⁶²

Scheme 3.4: Monoxime formation



It is well known that oximes are readily hydrolysed to the corresponding carbonyl compounds.¹⁴ The mechanism for this hydrolysis is highlighted in Scheme 3.5, and results in the observed 2-methyl-p-benzoquinone.

Scheme 3.5: Monoxime hydrolysis

The mechanism proposed above, not only explains the stoichiometry of the reaction, but also explains the observation that increasing concentrations of sulphuric acid, used as nitration catalyst, decreases the amount of 2-methylbenzoquinone. Sulphuric acid, a strong oxidant itself, would be expected to favour the formation of 2-methylbenzoquinone according to the oxidation mechanism of Scheme 3.2. However, the decrease in the amount of 2-methylbenzoquinone is easily rationalised in terms of a reduced tendency for the nitrosation in the presence of sulphuric acid. The formation of 2-methylbenzoquinone via hydrolysis of an initially formed nitrosophenol also explains why no o-benzoquinone is observed in these reactions, since nitrosation is always p-selective.³⁹

3.3.8 Nitrosation

It has been shown that nitrous acid may catalyse aromatic nitration. Some authors have even claimed that efficient nitration may be obtained through only nitrosation with subsequent oxidation of the nitrosophenol to the nitrophenol. It is also claimed that the nitrosation process is fairly rapid and that nitrosation favours p-nitrophenols.³⁸

3.3.8.1 Nitrosation using NaNO_2 and H_2SO_4

Ross, Hum and Blucher showed that para-selective nitration may be obtained with mixtures NaNO_3 and NaNO_2 in 50 – 60% H_2SO_4 . When they made use of only NaNO_2 with H_2SO_4 , they claimed to have obtained an o : p ratio of 0.03 : 1 of nitrophenol products.³⁹

This method was thus applied to the nitration of m-cresol to determine whether it would favour the formation of 4NMC (decrease in the o : p ratio). Changing the o : p ratio of m-cresol, as opposed to phenol, does present a greater challenge since the cresol does have a higher degree of substitution. Another factor that influences the ease of the regio-selectivity manipulation is the characteristics of the aromatic substituents. In this case, two activating o/ p-directors are located meta to one another.

A series of reactions were carried out to determine the effect of nitration via nitrosation on the o : p ratio. The reactions were all carried out at room temperature with constant stirring at 750 rpm. A stock solution of substrate in 1,2-dichloroethane was made up of which 20,00 cm³ was delivered to the reaction flask by burette. Two of the reactions made use of only NaNO₂ as nitrating agent with different amounts of sulphuric acid added. In these reactions, NaNO₂ was added in a 1 : 1 ratio to the substrate. In the third reaction, HNO₃, in a A : S ratio of 1 : 1, was used as nitrating agent with 10 mol % of NaNO₂ as catalyst.

Table 3.15: Nitration of m-cresol with NaNO₂

NaNO ₂ (g)	HNO ₃ (g)	H ₂ SO ₄ (g)	Conv (%)	Yield (%)	Account. (%)	Selectivity 4NMC (%)
0.2077 ^a	-	0.1544	14.5	0.60	86.1	41.7
0.2067 ^b	-	0.0298	16.0	12.7	96.7	41.7
0.0259 ^c	0.2819	-	96.2	90.0	93.8	43.4

^a – NaNO₂ : H₂SO₄ = 2 : 1

^b – NaNO₂ : H₂SO₄ = 10 : 1

^c – HNO₃ : NaNO₂ = 10 : 1

Results after 60 min reaction time

Nitrating agent : substrate ratio = 1 : 1

Acid concentrations: HNO₃ = 65%; H₂SO₄ = 98%

The results shown in Table 3.15, above indicate that the NaNO₂/ H₂SO₄ reaction is best carried out with a nitrating agent to acid ratio of 10 : 1. However, substrate conversions were very low, with no significant change in the 4NMC selectivity. Concentrated sulphuric acid was used undiluted in this study. The concentration of sulphuric acid used by Ross et al.³⁹ was in the range of 50 – 60%, which might have affected the results. It is possible that the substrate might have reacted with the sulphuric acid instead of the generated NO⁺ ions. The third reaction gave promising results, with a high selectivity for 4NMC.

In another experiment, the nitrosation was carried out by the addition of 2 mole equivalents of nitrosating/ nitrating agent (NaNO₂; 0.437 g; 6.33 mmol) per mole

of substrate (m-cresol; 0.348 g; 3.22 mmol). Internal standard (nitrobenzene; 3 mmol) was also added to the mixture. The reaction was carried out in 1,2-dichloroethane (20.00 cm³), while 60 % H₂SO₄ (10 cm³) was used to generate the NO²⁺ ions in solution. Samples were taken and analysed by HPLC as described in § 2.3.1.1 and § 2.4.2. The results for this experiment are summarised in Table 3.16.

Table 3.16: Nitrosation of m-cresol with 2 mole equivalents NaNO₂

N : S^a	Conv (%)	Yield (%)	Account. (%)	Isomer ratio^b
1.966 : 1	99.9	88.4	88.6	49.4 : 16.1 : 24.4 : 10.1

^a – Nitrosation/ Nitration agent : Substrate ratio

^b – order of isomers: 4NMC : 2NMC : 6NMC : 2-methyl-1,4-benzoquinone

The above results show an apparent increase in the selectivity to 4NMC, with an associated decrease in the selectivity to 2NMC and 6NMC. These results seem much better than those reported in Table 3.15. However, the third entry in Table 3.15 is primarily the cause of direct nitration (nitric acid was the nitration agent), whereas the results above could only have occurred via nitrosation.

3.3.8.2 Gas-phase nitrosation

In a patent by Smith and McGee,⁶³ it was claimed that a ratio of 21.6 : 1 of p : o nitro-products was obtained in the nitrosation and subsequent oxidation to nitrophenol. A yield of approximately 90 % nitrophenol was also claimed. The reaction system made use of two separate reaction flasks. In the first, generation of the oxides of nitrogen (mainly NO₂) was caused by the reaction of a strong acid with NaNO₂. The NO₂ gas was then swept, with the aid of N₂, into the second reaction flask. This flask contained sulphuric acid. The substrate, dissolved in acetic acid, was slowly added to the mixture from a dropping funnel. The nitroaromatic products could be formed immediately by adding dilute nitric acid to the sulphuric acid/ acetic acid mixture. This mixture was kept at a constant temperature of 0°C.

It was decided to apply this method to the nitrosation of *m*-cresol. In flask one was added 50 % H₂SO₄ (49 cm³; 0.351 mol). A solution of NaNO₂ (7.12 g; 0.103 mol) in approximately 40 cm³ water was added dropwise from a dropping funnel. The gasses were swept into the second flask by N₂. The temperature of this flask was maintained at 20°C. In the second flask was a mixture of 50 % H₂SO₄ (41 cm³; 0.292 mol) and 20 % HNO₃ (32 cm³; 0.113 mol). *m*-Cresol (11.3 g; 0.104 mol), dissolved in approximately 40 cm³ acetic acid was added dropwise to the acid mixture at approximately the same rate as that of the NaNO₂ mixture (added over about 90 minutes). The mixture was stirred vigorously and kept at a temperature of 0°C. After addition of the reagents was complete, the reaction mixture was left to stir for an additional hour at 0°C. Aliquots (0.5 cm³) were removed from the mixture before and after completion of the reaction, and diluted with 10 cm³ water. Nitrobenzene (0.100 g) was added to the sample before the organic phase was extracted with 10.00 cm³ ethyl acetate. These samples were further diluted with acetonitrile (0.5 cm³ with 2.5 cm³ CH₃CN), before HPLC analysis was carried out. Results from this experiment are given in Table 3.17.

Table 3.17: Gas-phase nitrosation of *m*-cresol

	This Work	Smith and McGee⁶³
Conversion (%)	99.7	nr ^b
Yield (%)	8.2	90.1
Accountability (%)	8.4	nr ^b
Selectivity 4NMC (%)	75.6	nr ^a
Selectivity 2NMC (%)	2.4	20
Selectivity 6NMC (%)	7.3	nr ^a
Selectivity 2-methyl-1,4-benzoquinone (%)	14.6	nr ^a
p : o ratio	8.2	21.6

^a – Phenol as substrate

^b – not reported

The results in Table 3.17 show very low conversion, yield and accountability. However, a very high p : o ratio was observed, yet still not in the same range as that reported. Lack of experimental experience in this relatively difficult-to-control reaction system might be the reason for the poor results obtained in our laboratories. It does, however, seem feasible that nitrosation might improve the relatively rigid selectivities to 4NMC reported throughout this work.

3.4 CONCLUDING REMARKS

The following remarks may serve as a summary of results obtained in this work.

- Nitration of m-cresol with dilute nitric acid in a stoichiometric ratio, in the presence of a lanthanide triflate such as yttrium(III)triflate, gave high conversions and yields with reasonable material balance. These results were, however, not significantly better than those obtained when the catalyst was absent from the reaction mixture. The percentage selectivity to 3-methyl-4-nitrophenol (4NMC) seemed marginally higher in mixtures where the catalyst was present; at the same time, there was an obvious loss in product accountability. It would thus seem that the catalyst does somehow promote nitration at the para position (relative to the OH group), but that it also catalyses side reactions, which lead to unquantifiable products. The catalyst is thus best omitted from the reaction mixture. A range of nitric acid concentrations may be employed for the successful nitration of m-cresol at low temperatures. Addition of yttrium(III)triflate extended this viable concentration range further. It was also found that at low temperatures, the triflate does in fact catalyse nitration, but high reaction temperatures and relatively high nitric acid concentrations masked this catalytic effect.
- From the results obtained from the experimental design, it may be concluded that the nitration of m-cresol with only dilute nitric acid in 1,2-dichloroethane is an extremely robust reaction, and that it may be successfully carried out

under a wide range of experimental conditions. The equations, which describe the second order response surface models were determined for the four reaction responses. Subsequently, the validity of these models was confirmed by analysis of variance and normal probability plots. Contour plots were then constructed for each of the reaction responses, where two variables were plotted against each other, the third being kept constant.

From these contour plots, it was shown that the temperature and nitric acid concentration does not have any significant effect upon the reaction responses, such as conversion, total yield, 4NMC selectivity and accountability. The acid to substrate ratio was found to be the only significant reaction variable, and accurately controlling this factor at a value of 1 : 1 gave the highest overall responses. The model did however indicate that the 4NMC selectivity and accountability responses might be slightly increased by working at a lower temperature and a lower acid concentration. This premise was tested by carrying out a series of reactions between 0 and 10°C, where the acid concentration was 39.4%. The A : S ratio was kept constant at 1 : 1. These reactions produced results as predicted by the experimental design. It was shown that conversion increased with temperature and that lower temperatures and concentrations increased the accountability and 4NMC selectivity. However, these improvements come at a cost: the substrate conversion is relatively low at these low conditions, and with low conversion is coupled low yield.

- Nitrations using clay supported nitrating agents could not be successfully applied in this study. It did, however, appear that “clayfen” had an apparent preference for para-nitration, whereas “claycop” exhibited a preference for the ortho-position.
- The nitration of m-cresol with mixed acid gave high conversions. However, the yield and material balance was very low. This was expected as these reaction conditions are very harsh and, with a highly activated substrate such

as m-cresol, often lead to by-products and tars. On the other hand, exceptionally high selectivity was obtained for 4NMC. Another interesting aspect to note is that almost no 2-methyl-1,4-benzoquinone was generated in this reaction.

- Nitration via nitrosation, in our hands, did not produce the expected results. The conversions and yields were very low. There did not seem to be any improvement in the selectivity of 4NMC. In the reaction where NaNO_2 was used as a catalyst, the results were comparable to nitration with 65% nitric acid in the absence of any catalyst. The 4NMC selectivity did appear to be higher in the case of the former. The gas-phase nitrosation was not very successful in terms of the observed conversion, total yield etc. It was, however, interesting to note that the selectivity to 4NMC and associated p : o ratio was far higher than in any of the other experiments. It seems thus that with some experience in this reaction, it could be possible to increase the p : o ratio.

It may hence be concluded that the nitration of m-cresol is best carried out with dilute nitric acid in a 1 : 1 ratio in the absence of a catalyst. The reaction mixtures so produced are clean and free of tars and other solids. Conversions are typically quantitative, with yields and accountabilities in excess of 90 %. The yield of 4NMC was routinely higher than 40 %. Of the alternative nitration methods used, only the mixed acid system produced comparable results.

CHAPTER 4

NITRATION OF p-CRESOL

4.1 INTRODUCTION

In comparison to the nitration of m-cresol, the nitration of p-cresol is considerably simpler in terms of the number of products which may form. Under conditions that result in mononitration only, there is only one product, namely 2-nitro-p-cresol. The only consideration in such a nitration process is to minimise dinitration and by-products arising from the oxidation of the methyl group by the nitrating mixture.

The amounts of products obtained from a reaction and also the quality of these products, in other words the yield and purity of products, are of major importance in large-scale production processes. At the same time, it is important to know the amounts of chemicals and raw materials charged in each process to yield these products. This information, termed the material balance, is extremely important in production economics for a number of reasons. Firstly, it is not cost effective to produce chemical products on an industrial scale when there is no indication of how much of each chemical is required, and how much product is expected. Secondly, chemistry in the hands of the ignorant can be extremely dangerous, as reactions often produce heat, which may cause the reaction to run away; sometimes even toxic or explosive mixtures may form.

The process chemist has always been equipped to answer nearly all questions relating to the material balance. These answers may be found by an intimate study of the reaction mechanism and stoichiometry. Many reactions, though, do not proceed through discrete reactant ratios; it is then especially necessary to establish the rates of reactions relative to the various reactants and products.

The construction of product distribution curves is often helpful in determining the rates of reaction. Of course, short reaction times (high reaction rates) also imply quicker batch turnovers, which in turn implies higher production volumes.

Once the rate of reaction is established, it is prudent to determine the product yields and product purity. This implies that the product must be removed, or isolated, from any impurities that might be present in the reaction mixture, such as side products and reaction solvent, and then to subsequently determine its purity. It is often necessary for the chemist to make use of purification techniques such as extraction, recrystallisation and distillation to eventually obtain an adequately pure product. Of course, if the reaction route is ever to become an industrially viable process it is important for the chemist to select isolation methods that may be carried out on industrial scale, which means that cost effectiveness and safety should also be taken into consideration.

Nowadays, chemists are under increasing pressure to obtain higher yields and conversions in shorter times. At the same time, it is compulsory to obtain these results by making use of what is currently known as “green” chemistry. Concern for our environment is growing; it has become imperative to counter the damage that was done by over-zealous industrialists in the fifties and sixties. It is thus important for the chemist to minimise the wastes generated in a chemical process. The reaction wastes also need to be identified and quantified.

Traditionally, the chemist’s involvement would end with an intimate knowledge of the reaction mechanism and the material balance, and the chemical engineer would then take over. It was always the engineer’s function to determine the energy balance of a reaction; in other words the amount of energy that must be added through heating etc. to initiate the reaction, how much energy is produced during the reaction and the amount of energy that has to be removed through cooling during the reaction to keep the process safe. Also included in the energy balance is the internal energy of each reactant. Another very important factor is the amount of heat lost through the reactor material to the environment. This information was required for scale-up purposes, since energy in a “world-scale”

production plant may be treated as a commodity, and heating and cooling of any reaction mixture increases the unit price of a chemical product. Cost efficiency is not the only reason why knowledge of the heat balance is required. Heat evolved in a chemical reaction also has a serious implication in terms of the safety of plant personnel, as plant equipment and certain chemicals have a specified safe working range.

The skill associated with determining the energy balance of a chemical reaction has become accessible to the modern process chemist. Through a thorough knowledge of reaction thermodynamics and making use of techniques such as reaction calorimetry, it has become possible for the chemist to gain a lot more information concerning a specific reaction.

4.2 OBJECTIVES

The objectives for this part of the investigation may be summarised as follows:

- **To nitrate p-cresol with dilute nitric acid and to determine the product distribution diagrams for each of the mono- and dinitration steps.**
- **To determine whether the two steps proceed discretely or if they occur concurrently.**
- **To increase the scale of the reaction and to isolate the product, as well as to determine the purity of the product.**
- **To identify the waste generated during the reaction and to quantify it.**

4.3 RESULTS AND DISCUSSION

4.3.1 Mono- and dinitration of p-cresol

p-Cresol and nitrobenzene (internal standard) were made up in a stock solution with either 1,2-dichloroethane or iso-propanol. This stock solution was run into a reaction vessel by means of a burette (20.00 cm³; 3.0 mmol p-cresol and nitrobenzene). 65% HNO₃ was weighed into reaction mixture (0.29 g; 3.0 mmol) with a microsyringe and the reaction mixture placed in a temperature bath at 60°C with constant stirring at 750 rpm. The mixture was left to react for 15 minutes, before samples were taken and submitted for HPLC analysis (§ 2.3.1.1 and § 2.4.2). The results for the separate reactions are given in Table 4.1.

Table 4.1: Mono- and dinitration of p-cresol

Rxn. No.	Solvent	[Acid] %	A : S	Conv. (%)	Yield 2NPC ^a (%)	Yield DNPC ^b (%)	Account. (%)
1.	DCE	65	0.959 : 1	100	95.8	-	95.8
2.	DCE	65	1.958 : 1	100	-	97.5	97.5
3.	DCE	93	1 : 1.014	100	92.4	4.5	96.9
4. ^c	DCE	93	1 : 0.989	100	94.3	2.2	96.5
5.	i-PrOH	65	1 : 1.002	7.0	6.6	-	99.6
6.	i-PrOH	93	1 : 0.985	54.9	53.8	-	98.8
7. ^c	i-PrOH	93	1 : 0.968	42.2	39.0	-	96.8

^a – 2NPC – 2-nitro-p-cresol

^b – DNPC – 2,6-dinitro-p-cresol

^c – Reactions done at 5°C.

The nitration of p-cresol resulted in the desired nitrocresol products in excellent yields when using 1,2-dichloroethane as reaction solvent. Using a higher acid concentration resulted in the formation of small quantities of dinitrated products during mononitration. The accountability of the nitration reaction was excellent in all cases. Two reactions (reactions 4 and 7) were carried out at lower reaction temperatures, but without affecting the reaction outcome too drastically.

4.3.2 Effect of substrate loading

Several experiments were also carried out at higher substrate loadings (the reactions shown in Table 4.1 were carried out at low (1.7 %) substrate loading). In this study, 93 % (m/m) nitric acid was used as nitration agent. The substrate and internal standard were weighed into the reaction flask containing 20.00 cm³ 1,2-dichloroethane. The nitric acid was added to the mixture over a period of one minute, after which the mixture was immersed in an ice bath at 5°C. Timing of the

reaction was commenced as soon as the first drop of nitric acid came into contact with the substrate/ solvent mixture. The mixture was left to react for 15 minutes before a sample was taken. The results of these experiments are summarised in Table 4.2.

Table 4.2: Effect of increased substrate loading

Rxn. No.	Loading (% m/v)	A : S	Conv. (%)	Yield 2NPC ^a (%)	Yield DNPC ^b (%)	Account. (%)
1.	1.7	1 : 1.014	100	92.4	4.5	96.9
2.	4.9	1 : 0.996	100	86.0	3.7	89.7
3.	8.1	1 : 0.995	96.7	79.5	6.3	89.1
4. ^c	16.2	1 : 1.250	91.4	43.7	30.4	82.6

^a – 2NPC: 2-nitro-p-cresol

^b – DNPC: 2,6-dinitro-p-cresol

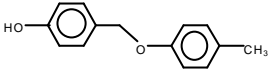
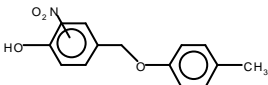
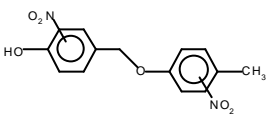
^c – Mixture boiled before nitric acid addition was complete

A number of observations from these results are of interest. Firstly, there is a significant decrease in the conversion as the substrate loading is increased from 1.7% (m/v) to 16% (m/v). These reactions were terminated after a reaction period of 15 minutes. Secondly, despite the fact that the acid : substrate ratio was kept close to 1 : 1, there

is a significant increase in the yield of dinitrated product. This clearly suggests a rapid reaction of the initially formed mononitrated product due to the presence of a local excess of acid in the reaction mixture. The last observation relates to the observed decrease in reaction accountability as the substrate loading is increased.

The chromatograms obtained from the HPLC analyses (Appendix 4.1) for these reaction mixtures indicated the formation of a number of side products. These were investigated using mass spectrometry, a total of five different by-products being observed in the GC-trace (Appendix 4.2). The mass fragmentation patterns of the individual compounds (three of the five could be elucidated) were used to assign identity to the individual by-products. These assignments are summarised in Table 4.3.

Table 4.3: GC-MS assignments for the by-products obtained in the p-cresol nitration

No.	T _r (min)	Area % (TIC)	Proposed Structure	Mm (g.mol ⁻¹)	Fragmentation
1	18.4 4	2.4		214	M⁺ (214); M-15 (CH₃[•]); C₆H₅CH₃⁺ (91); Tripylium (91); HOC₆H₄CH₂O⁺ (122)
2	21.5 2	74.9		259	M⁺ (259); M-17 (OH[•]); Tripylium (91); M-151 (OC₆H₃(NO₂)CH₂[•])
3	24.9 3	17.1		304	M⁺ (304); M-17 (OH[•]); M-46 (NO₂[•]); HOC₆H₃(NO₂)CH₂⁺ (153)

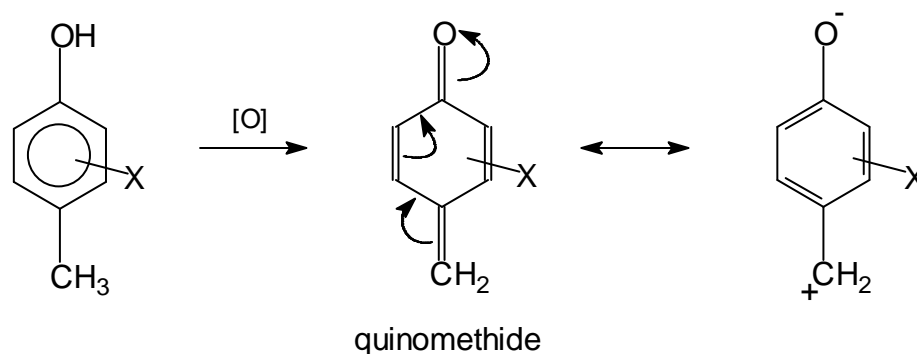
From the tentative assignments made in Table 4.3, it can be seen that by-product formation is mainly the result of oxidation of the aromatic ring, most probably to give an initial quinone methide intermediate, which then undergoes nucleophilic addition with either unreacted substrate or nitration product. Possible mechanisms of formation for these by-products are given in Scheme 4.1. High acid concentrations and high substrate and/ or product concentrations will obviously favour these reactions.

In other oxidative work carried out on p-cresol in our laboratories,⁶⁴ similar dimers, to those shown in Table 4.3 (compounds with Mm. 214, 259 and 304), were also observed. Their formation was explained in terms of nucleophilic addition of p-cresol or the respective nitro-substituted products to quinomethide or nitro-substituted quinomethide. It has previously been reported that quinomethides do exist as intermediates

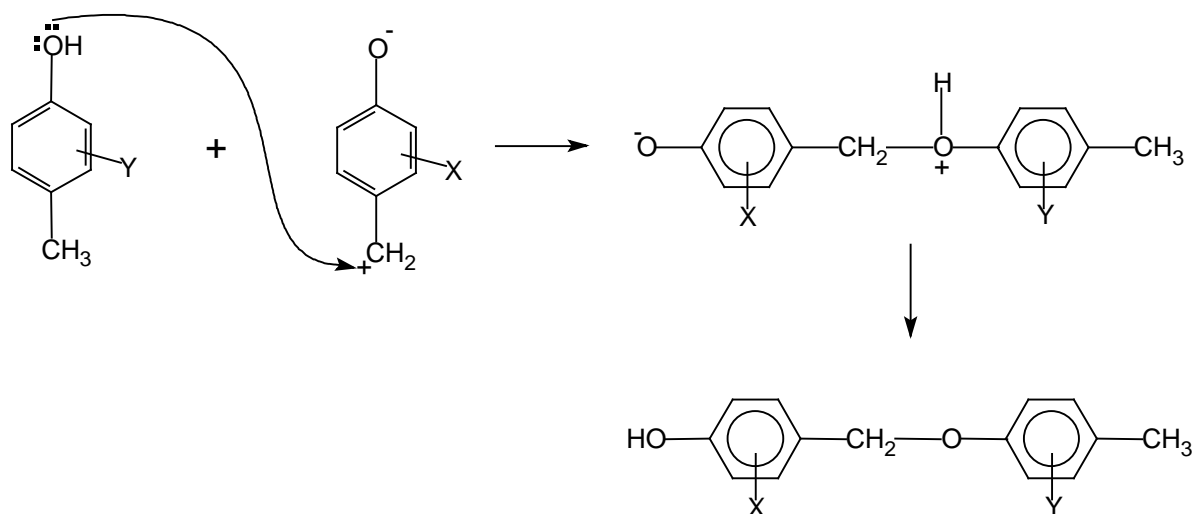
under oxidising conditions with p-cresol as substrate.^{65,66}

The mechanism for the formation of these dimers may hence be envisaged to follow a similar route to that described previously,⁶⁴ i.e. p-cresol or nitro-p-cresol is oxidised to the respective quinomethide which then undergoes nucleophilic attack by another similar compound (Scheme 4.1).

Scheme 4.1: Dimer formation



Scheme 4.1: continued...



For compound Mm. 214, X = Y = H
 For compound Mm. 259, X = NO₂, Y = H
 For compound Mm. 304, X = Y = NO₂

The exact identity of ether with Mm. 259, whether the nitro group is attached to the hydroxy-substituted ring or the methyl-substituted ring, cannot be ascertained using the techniques available to us.

Despite the formation of these by-products, the direct nitration of p-cresol to either mono- or dinitrated product appears quite attractive since high yields and accountabilities are possible. The formation of by-products, including DNPC during the mononitration of p-cresol, seems controllable in terms of acid concentration, substrate loading and rate of acid addition. The results obtained indicate that the mononitration product is sufficiently deactivated towards further attack to ensure that all of the substrate is first converted before the dinitration step commences. This implies that the mono- and dinitration reactions proceed as separate steps and that the formation of DNPC can be effectively minimised by careful control of the experimental variables referred to above.

4.3.3 Scale-up of p-cresol nitration – isolation of reaction product

In order to study the isolation of 2NPC formed during the direct nitration of p-cresol, it was necessary to increase the scale of the substrate load in the reaction to facilitate the subsequent product isolation and purification of 2NPC. The reaction was carried out in a 250 cm³ three-necked round-bottomed flask with 1,2-dichloroethane (150 cm³) as solvent. p-Cresol (19.6 g; 181 mmol) was added to the solvent and the solution stirred at 60°C. Nitric acid (65%; 18.3 g; 191 mmol) was added dropwise over a period of 60 minutes. After the acid addition was complete, the reaction was left to stir for an additional two hours to complete the reaction. At this point, the reaction mixture was poured over ice, the phases separated and the organic layer extracted into ether. The solvent was removed by distillation. The crude product was weighed and set up for steam distillation with internal steam generation. The product was subsequently extracted from the water phase with ether and the solvent was removed by vacuum distillation.

The product, a golden yellow solid with a distinctly nitro-aromatic odour, was weighed, and analysed by HPLC and GC-MS (§ 2.4.2 and § 2.4.3 respectively). Table 4.4 summarises the results obtained in this experiment.

Table 4.4: Scaled-up nitration of p-cresol

Acid to substrate ratio	1 : 0.950
Mass of crude product (g)	24.86 50
Isolated yield (g)	10.23 42
Analytical yield (g)	13.13 36
Purity of pure product (%)	99.9
Isolated yield (%)	36.9
Analytical yield (%)	47.3

Mass spectrometric and H-NMR (Appendix 4.3 and 4.4) analysis proved that the isolated product was indeed 2NPC. The purity determined with the aid of HPLC, using the internal standard method, showed that the steam distillation was effective in purifying the crude product. Although the isolated yield is low, it compares well with the HPLC yield obtained for these reactions. Analysis of the residue from the isolation step by GC-MS showed the same by-products found previously (compounds in Table 4.3), together with small amounts of dinitrated product. These results seem to indicate that careful control of the acid addition rate alone will not be sufficient to obtain good results due to the rapid nature of the reactions in question (nitration, dinitration and oxidation).

Two further reactions were carried out at these high substrate loadings: in the first, acid was fed to the reaction mixture containing all the substrate in the 1,2-dichloroethane solvent and in

the second, acid and substrate were fed simultaneously to the reactor containing half the amount of reaction solvent. Use was made of the Simular reaction calorimeter for the purposes of using the dosing pumps, for better process control. Details of the operation of this instrument are given in § 2.3.2 and § 5.3.1. Calorimetric data obtained in these reactions will also be discussed in § 5.3.

In the first reaction p-cresol (40.0 g; 370 mmol) was weighed into the glass liner containing 1,2-dichloroethane (250 cm³). Nitric acid (65%; 35.6 g; 371 mmol) was fed to the reactor at 0.5 g.min⁻¹.

In the second reaction, the acid to substrate ratio of 1 : 1 was maintained throughout. The reactor contained 155 g of 1,2-dichloroethane prior to the addition of any other reactants. 194 g of a mixture containing p-cresol (80.9 g; 748 mmol) in 1,2-dichloroethane (309 g) was dosed to the reactor at a rate of 2.73 g.min⁻¹ over approximately 71 minutes. Nitric acid (65 %; 35.5 g; 370 mmol) was simultaneously dosed at a rate of 0.5 g.min⁻¹.

Samples were taken from the reaction mixture and analysed with the aid of HPLC. The sampling procedure may be summarised as follows: 0.5 cm³ aliquots were removed from the reaction mixture; nitrobenzene (0.45 g) was added to all samples prior to further dilution with 5.00 cm³ acetonitrile. After completion of the reactions, products were isolated in exactly the same manner as described earlier in this section (§ 4.3.4). Results from the scaled-up reactions are summarised in Table 4.5.

Table 4.5: Additional scaled-up p-cresol nitrations

Reaction	A : S	Conv. (%)	Yield 2NPC (%)	Yield DNPC (%)	Account. (%)
1 ^a	1 : 0.999	96.8	53.5	0.2	56.9
2 ^b	1 : 0.994	92.2	56.3	2.4	66.6

^a – dosing of nitric acid only

^b – dosing of both nitric acid and substrate/ solvent mixture

2NPC: 4-methyl-2-nitrophenol

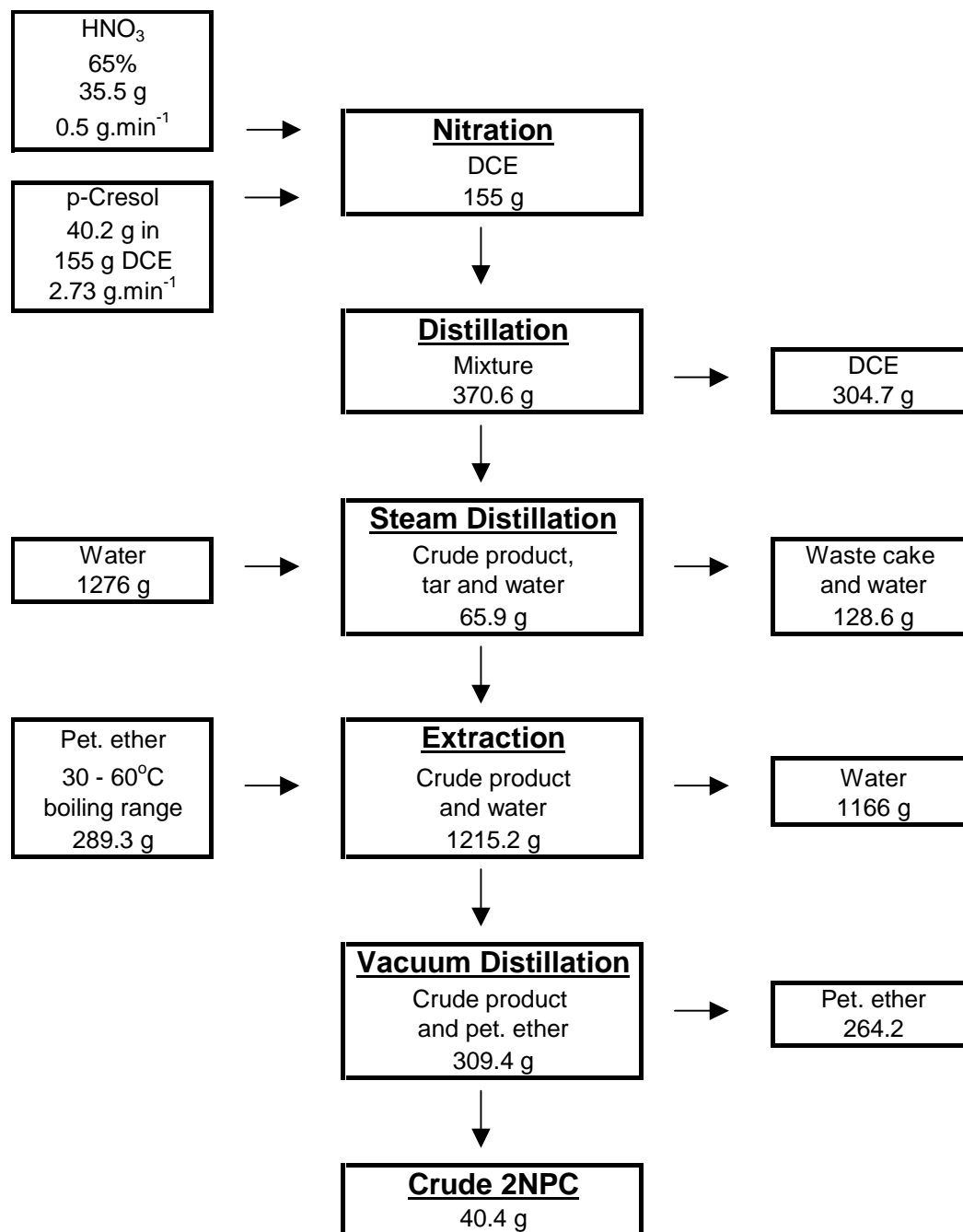
DNPC: 2,6-dinitro-p-cresol

The results obtained for experiment 1 confirm that the control of acid addition rate alone will not be sufficient to ensure high yields of the desired product. The results obtained for this experiment compare closely to the results obtained previously (Table 4.4). The findings for the second experiment, in which both the acid and the substrate were fed simultaneously to the reactor, however, were considerably better and clearly showed that with slower addition rates and better mixing, excellent results may be achieved at high substrate loading.

All reagents, solvents (aqueous and organic), as well as products and waste products, obtained

from reaction 2 (Table 4.5) were weighed. This information was used to construct a detailed mass balance, given in Figure 4.1.

Figure 4.1: Mass balance for the nitration of p-cresol



The mass balance of this reaction gave a crude yield of 40.4 g of 2NPC; however, an analytical yield of approximately 56 % was obtained. It may be

concluded that the product still needs further purification. It does seem that the isolation method (steam distillation) is efficient enough to remove most of the 2NPC that was produced in the reaction since the percentage recovery (isolated yield/ analytical yield) was consistently higher than 75 %. Losses did however occur when considering the system as a whole. Evaporation of solvents, especially low boiling solvents such as petroleum ether, could account for some of the material losses. Furthermore, small amounts of 2NPC are soluble in water, and hence some of the material may have been lost in the extraction step. Therefore, even though most of the reaction material seems to be accounted for, some losses did occur which would have to be minimised even further if a process such as this was ever to be carried out on a production scale.

4.4 CONCLUDING REMARKS

- The mono- and dinitration of p-cresol produced the expected products. Nitration in 1,2-dichloroethane yielded very promising results (yields and accountabilities higher than 90 %), whereas nitration in iso-propanol gave very poor results, only 55 % conversion with 93 % nitric acid at 60°C. Higher acid concentrations resulted in the formation of greater amounts of dinitrated products. The mono- and dinitration reactions proceed as separate steps, since no DNPC was observed in the mononitration under properly controlled conditions.
- The substrate loading (m/v) was found to have great influence on the reaction accountabilities. The substrate conversion decreased and the amount of DNPC increased with an increase in the substrate loading, even when the A : S was carefully controlled at 1 : 1. This means that stirring and slow addition is very important in the nitration reaction to avoid the formation of local excesses of acid. GC-MS analysis of the waste products revealed the formation of a number of ether dimers of cresol and nitrocresol. These

products are probably the result of oxidation taking place in the reactor at the same time as the nitration process.

- The nitration of p-cresol was scaled-up to facilitate the isolation and purification of 2NPC. The reaction where nitric acid (18.3 g) was added to p-cresol (19.6 g) in 1,2-dichloroethane gave a very low material balance and isolated yield (approx. 37%) and analytical yield, while the purity of the isolated product was found to be 99.9 %.
- Two further scale-up reactions were carried out, one with a final A : S ratio of 1 : 1 and the other where the A : S ratio was maintained at 1 : 1 throughout the reaction. Results clearly showed that the accountability and yield (analytical) were higher in the second case. This is thought to be the result of better mixing and slower addition. A mass balance was constructed for the second reaction through the separation of product, solvents and waste. This also indicated that the isolation method is efficient for the separation of the product. However, some losses did occur when considering the process as a whole, and some material could ultimately not be accounted for.

CHAPTER 5

HEAT OF p-CRESOL NITRATION

5.1 INTRODUCTION

Reaction calorimetry is a relatively new technique that is available to the modern process chemist. It is a powerful tool for the determination of a number of thermodynamic properties of batch and semi-batch processes required for the scale-up of chemical reactions. Organic processes traditionally went through a number of stages between the lab-scale and production scale, before production plants could be erected. The reason for this is that many properties of a chemical reaction are often found to be scale-dependent. The most important property that needs to be dealt with effectively is the heat generated by the chemical reaction. The laboratory chemist can effectively deal with heat generated in a lab-scale reaction by removing the

heating source and possibly adding ice to the mixture. However, on a production facility, cooling and heating systems need to be designed for the removal/ supply of much larger amounts of heat. For this, an accurate knowledge of the total amount of heat generated, as well as the rate of heat generation, is required.

Conventionally, the different stages in a process scale-up included: initially small lab-scale reactions with the production of a few grams of product; this then was increased to kilogram-scale in a process laboratory. The process chemist carried out these steps. After this would follow pilot-scale reactions where the problems associated with production would first appear, since use would be made of steam and chilled water for heating and cooling, respectively. Pilot reactors are typically between ten and 100 litres. After this would follow the Com-Dev stage (commercial development) where the problems associated with heating and cooling are normally

even larger, and thus more representative of those experienced on large production plants. The scale in this case would be very close to production plant-scale, and generally the same types of reactors would be used. This stage was normally carried out exclusively by chemical engineers and gave them the very last chance to ensure that the reaction system was safe and could be carried out successfully on a production scale plant. After this, once all the parties involved with the development of a specific process were satisfied that the system was safe and cost effective, it was introduced to the final stage, which was the actual production stage.

However, with the advent of reaction calorimetry, it has become possible for a process chemist to determine the energy characteristics at the lab-scale stage. It is thus possible to shorten the pilot trials for some processes and in some cases to even eliminate them completely.⁶⁷⁻⁷⁰

Batch chemical reactions can be conveniently studied in reaction calorimeters. These devices are based on conventional jacketed laboratory reactors, and can provide invaluable information concerning the safety and operability of a process. A typical reaction calorimeter is shown in Figure 5.1, illustrating the fact that the system is basically a computer-controlled pilot reactor system, from which thermal data may be obtained. Reaction calorimetry allows the heat output rate, Q_r , for a reaction to be determined from a heat balance across the reactor wall, given in Equation 5.1:

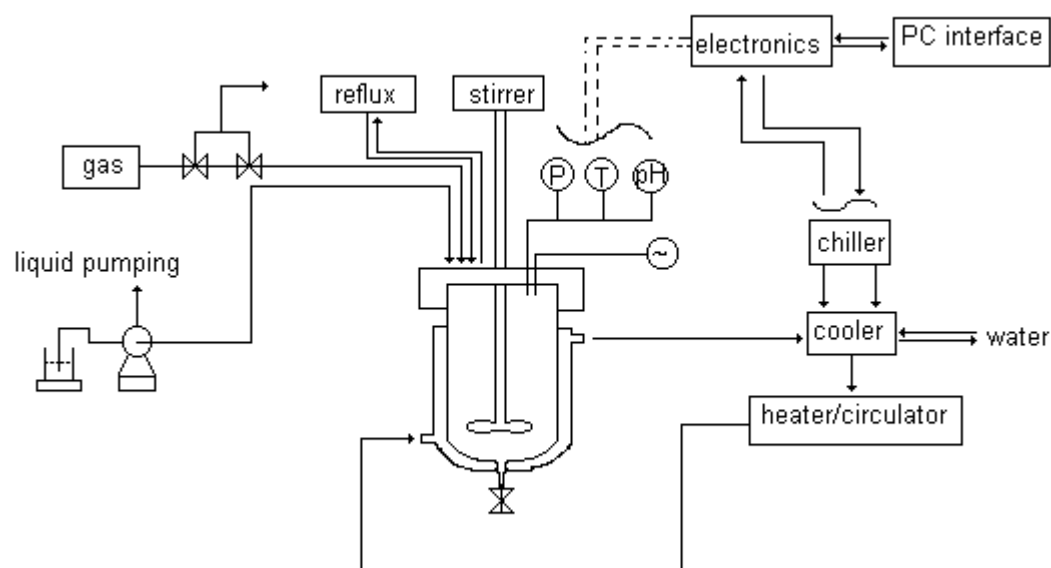
$$Q_r = Q_{rem} + Q_L + Q_{accum} + Q_{dose} \quad \text{Equation}$$

5.1

where Q_L is the heat loss from the vessel, Q_{rem} the heat removed (or added) by the oil circulating around the vessel jacket, Q_{accum} is the sensible heat (if any) being accumulated by the reactants

and the reactor, and Q_{dose} is the heat taken up by the feed (if any).⁷⁰

Figure 5.1: Reaction calorimeter flowsheet⁶⁸



5.1.1 Heat flow method

The heat flow method is the most common of all reaction calorimetry methods, where Q_r information is obtained from knowledge of heat transfer through the reactor walls to the coolant circulating through the vessel jacket. Heat flow, Q_r , is calculated using Equation 5.2 in this case:

$$Q_r = UA\Delta T \quad \text{Equation 5.2}$$

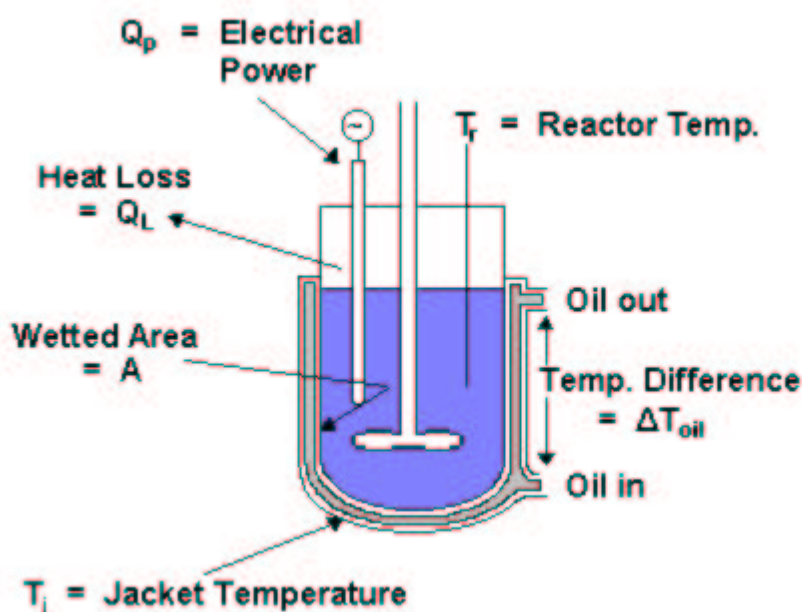
where U is the overall heat transfer coefficient, A the wetted area, and ΔT the difference in temperature between the reactor and jacket. Application of heat flow calorimetry requires that UA be determined for every experiment. This term usually also varies during the course of the reaction, as the composition of the mixture changes during the reaction. It is thus necessary that UA be calculated at least twice, usually at the beginning and end of each experiment, with interpolation between the two. This leads to a number of problems:

- inaccuracy caused by the need to interpolate;
- long experimental time to obtain UA ;
- little, or no, information about the variation of UA during the reaction.⁶⁷

5.1.2 Power compensation method

An improved method compared with that highlighted above has recently been developed, which simplifies the experimental procedure while improving the final result of the experiment. The experimental arrangement for this approach is shown in Figure 5.2.

Figure 5.2: Main variables used in reaction calorimetry



Here the reactor is controlled at a temperature T_r and the oil temperature entering the jacket is fixed at T_j ; the difference in temperature between the oil inlet and the oil outlet is ΔT_{oil} . A calibrated heater inside the reactor controls the reactor temperature at T_r , compensating for heat removal through the jacket, heat loss and reaction heat output.

At the start of an experiment under steady state, before the reaction begins (i.e. $Q_r = 0$), a heat balance around the reactor may be summarised by Equation 5.3:

$$Q_p(o) = Q_{rem} + Q_L \quad \text{Equation 5.3}$$

where $Q_p(o)$ is the heat into the vessel from the electrical heater necessary to maintain T_r , and is known as the “baseline” power. If a reaction begins, releasing Q_r , the electrical power (Q_p) would have to be reduced to maintain a constant reactor temperature (Equation 5.4):

$$Q_p = Q_p(o) - Q_r \quad \text{Equation 5.4}$$

In the case of power compensation calorimetry, no calibration (UA determinations in heat flow mode) is needed, and reaction heat is obtained directly from the baseline power ($Q_p(o)$) and the power at any given time, Q_p . The use of power compensation calorimetry has a number of advantages over heat flow calorimetry. Experiments are generally faster and easier to set up, since calibration steps may be omitted from the experimental plan. Interpretation of data is also much simpler. Since control of the reactor temperature is by means of a heater immersed directly in the reaction liquid, control is both fast and accurate. The main disadvantage with this method becomes apparent when very highly viscous liquids are processed. Temperature control becomes poor and reaction material may “cake” on the heater element.⁶⁷

5.1.3 Reflux flow method

Many industrially important reactions are performed by allowing the reactants to boil and removing heat through an overhead condenser. This can be studied using a reaction calorimeter and involves a heat balance across the condenser in order to obtain the reaction heat output rate, Q_r , given in Equation 5.5:

$$Q_r = c_{pc} M_c (\Delta T_r - \Delta T_b) \quad \text{Equation 5.5}$$

where M_c is the coolant flow rate through the condenser, c_{pc} its specific heat, ΔT_r the increase in the coolant temperature during the reaction between condenser inlet and outlet, and ΔT_b the increase in the absence of reaction (i.e. the baseline). Practically the reaction mixture is brought to the boil and allowed to equilibrate at the boiling temperature to ensure a stable baseline. When the reaction is started, the changes in ΔT_r are mostly due to the reaction exotherm (or endotherm). Since this form of calorimetry is also dependent on the UA of the reactor, calibration steps also need to be performed before and after a reaction.⁶⁷

5.1.4 Typical applications

- Progress of reaction

In very simple terms, it is normally correct to assume that the rate of reaction is proportional to the heat output rate (power). This enables very simple but accurate judgements to be made on batch times needed. It is a very common way of optimising batch operation without any initial analytical work.

- Reaction rate

The rate of heat output, Q_r , measured in a calorimeter is proportional to the reaction rate. This can be very valuable, even without knowing the actual rate constants.

- Mixing studies

A well-controlled reactor, which can indicate heat output, can also be very valuable in studying multi-phase reactions where the extent of mixing is

crucial. Induction periods can be identified with these instruments, since the reaction onset can be identified from the power output.

- **Process safety**

Knowing the heat output rate, Q_r , the cooling duty for the scaled-up process can be directly specified. This is very important design information, but also has a significant bearing on the safety of the system. The reaction enthalpy may be used to obtain the theoretical adiabatic temperature rise, ΔT_{ad} . This is a useful parameter, although not entirely sufficient to define the extent of the hazard. A knowledge of reactant accumulation is a much more valuable parameter. Accumulation is essentially a direct result of slow initial reaction rates. As more reactants are dosed into the reactor, a build-up of this unreacted material occurs. There is thus also an accumulation of potential energy in the reactor. When the reaction is set off, large amounts of energy is released, and even if fresh feed to the reactor is stopped, the danger cannot be averted. This leads to, what is known as, a runaway reaction.⁶⁷

5.2 OBJECTIVES

The objectives for this chapter may be summarised as follows:

- The use of the Simular Reaction calorimeter to determine the heat evolved in a nitration reaction.
- To investigate the influence of the substrate loading in a scaled-up reaction.
- The use of calorimetry to investigate the influence of catalysts on the heat of reaction as well as the mechanism of nitration.
- To determine the effect of nitric acid concentration on the heat of reaction.

5.3 RESULTS AND DISCUSSION

5.3.1 Nitration of p-cresol using the reaction calorimeter

A similar reaction was discussed in the previous chapter (§ 4.3.3 and Table 4.5, experiment no. 1). However, the calorimetric data obtained were not discussed. This chapter thus concentrates on the thermodynamic properties of the p-cresol nitration reaction.

This instrument (reaction calorimeter) was operated in the power compensation mode at 50°C (§ 2.3.2). p-Cresol (40.0 g; 0.370 mol) was weighed into the glass liner containing 1,2-dichloroethane (250 cm³). Nitric acid (65 %; 35.6 g; 0.370 mol) was dosed to the reactor at 0.5 g.min⁻¹. The power output (a function of heat of reaction in power compensation calorimetry) of the reaction was observed until it had returned to the baseline value, which indicated that the reaction was complete. The reaction mixture was poured over ice and the phases separated. The organic layer was extracted into ether and the solvents removed by vacuum distillation. The crude product was weighed and set up for steam distillation. The product was subsequently extracted from the water phase with ether and the solvent was removed by vacuum distillation. A sample of the product (4-methyl-2-nitrophenol) was analysed by HPLC. The results of this reaction are given in Table 5.1. Figure 5.3 shows a typical energy plot observed for the nitration of p-cresol, using the reaction calorimeter.

Table 5.1: Calorimetric nitration of p-cresol

Acid to substrate ratio	1 : 1.002
Mass of purified product (g)	26.13
Purity of purified	95.8

product (%)	
Isolated yield (%)	45.9

The energy report, generated with the aid of HEL Wincalc software, gave the following results:

Total Flow/ Balance Energy = 57.36 kJ

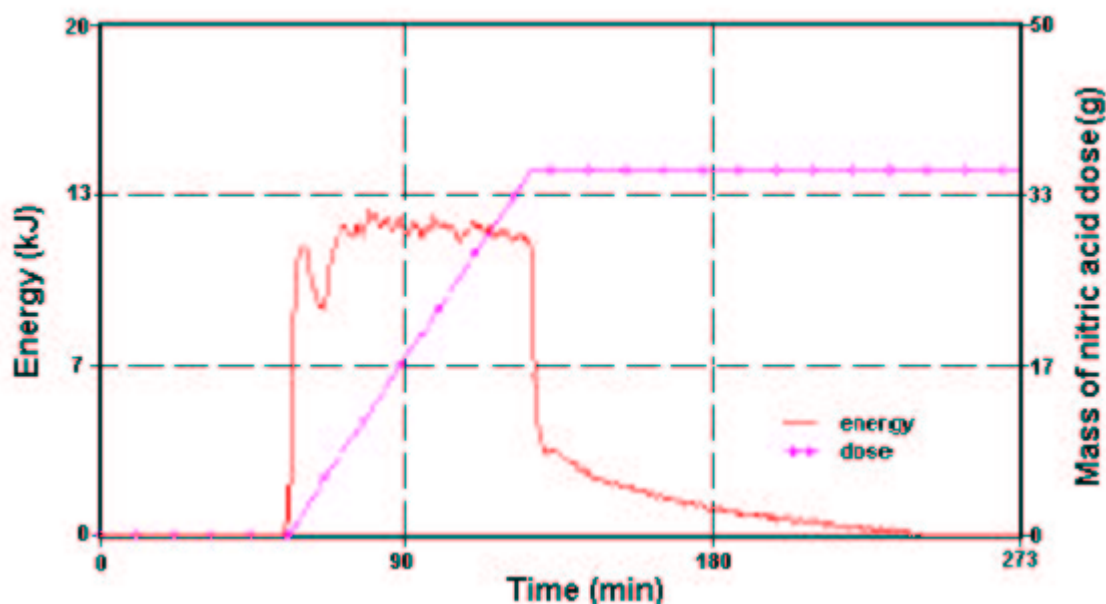
Total Dose Energy = 1.25 kJ

Total Accumulation Energy = 0.00 kJ

Equals a Total Energy of 58.61 kJ

Molar Heat: -103.67 kJ based on the addition of 36.63 g 65 % nitric acid

Figure 5.3: Energy plot for the nitration of p-cresol with 65 % nitric acid



The energy plot shows that the nitration process is almost instantaneous; no induction period was observed under these reaction conditions. A sharp peak (reaction exotherm) is observed as soon as nitric acid addition commences, which was also associated with the evolution of a brown gas (NO_2) from the top of the condenser. During this period, the power supply to the internal reactor heater is practically suspended. After this initial exotherm is completed, the reaction proceeds “smoothly”, and the heater has to turn on again before the

nitric acid feed is terminated. Little heat is evolved after nitric acid addition is terminated, indicating no significant build-up of unreacted reagent in the reactor, a situation known as accumulation. The heat of reaction obtained for this reaction was -103 kJ/mol , which indicates that aromatic nitration is a highly exothermic process, with a large amount of energy being released during the reaction. Of particular concern, however, is the very sharp rise in temperature at the start of the reaction, which could prove problematic if cooling and feed control is lost during this stage of the reaction.

Since the yield of 4-methyl-2-nitrophenol (2NPC) was again very low, it was decided to repeat the reaction on the calorimeter, this time with regular sampling to allow the construction of a product distribution diagram. This would indicate the concentration changes of the various species in the reaction mixture at specified times during the reaction. The quantities of chemicals and reaction variables used in the second calorimetric experiment were kept the same, as far as possible. In this case, 0.5 cm^3 aliquots were removed from the reaction mixture at regular intervals. Nitrobenzene (0.45 g) was added to all samples prior to further dilution with 5.00 cm^3 acetonitrile. The samples were taken at intervals of 14 minutes, with a total reaction time of 71 minutes (35.6 g of nitric acid dosed at 0.5 g.cm^{-1}). The mixture was left to stir for an additional period to allow completion of the nitration process. During this period, the power output of the internal calibration heater was carefully observed to ensure that the baseline power was achieved (indicating that the exothermic process was concluded). The results obtained in this experiment are summarised in Table 5.2, while the product distribution diagram is illustrated in Figure 5.4.

Table 5.2: Some results in the second calorimetric nitration

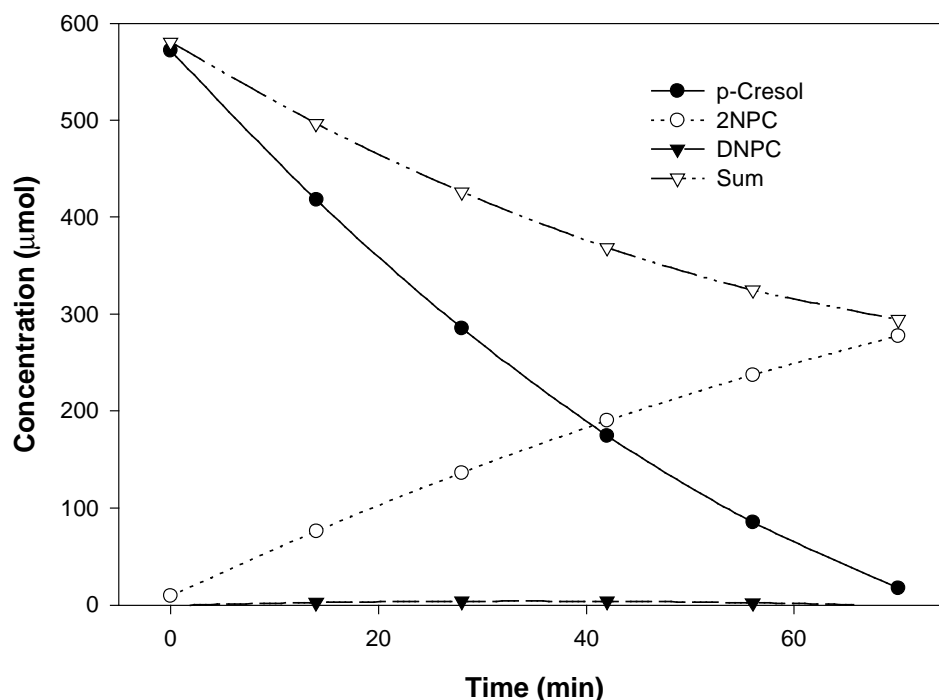
Reaction time (min)	Conv. (%)	Yield 2NPC (%)	Yield DNPC (%)	Account. (%)
70	96.8	53.5	0.2	56.9
98	98.3	48.5	0.1	50.4

A : S ratio – 1 : 0.999

2NPC – 4-methyl-2-nitrophenol

DNPC – 2,6-dinitro-p-cresol

Figure 5.4: Product distribution diagram for a scaled-up nitration of p-cresol



It is clear that the low material balance is the result of the conversion of the substrate into the by-products identified previously (§ 4.3.2). The product distribution diagram shows that the accountability decreases consistently during the reaction, even while the required product (2NPC) is forming during the reaction. There are thus competing processes taking place simultaneously in the reaction mixture. After completion of the reaction, the final accountability is less than 50 %, which means that more than 50 % of the reaction mass is due to side products, most probably as a result of the oxidation of the methyl group by nitric acid.

The reaction mass was collected and subjected to steam distillation, this time not to obtain the purified nitrocresol product, but the waste products (reaction tars etc.) responsible for the low material balance. The tar obtained, after removing

the nitroresol by steam distillation, was dried in an oven at 110°C to remove the water and organic solvent. This yielded a dark brown “syrupy” mass, which solidified into a brown porous cake upon cooling. The tar was weighed and analysed by GC-MS. By-products, analogous to those discussed in § 4.3.2, were again found. The results for the analysis of the reaction by-products are given in Table 5.3.

Table 5.3: Effect of by-product formation on accountability

Mass of tar (g)	26.2
Analytical yield of 2NMC (g)	27.5
Total mass (g)	53.7
Theoretical yield (g)	56.8
Analytical accountability (%)	50.4
Total accountability (%)	94.5

The above results show how the formation of waste products and tars has a clearly detrimental effect on the accountability of the reaction. When the tars are added to the isolated product, the material accountability increases dramatically from 50.4 to 94.5 %.

5.3.2 Effect of substrate loading

The material balance from the previous calorimetric run was very low, causing some doubt as to ascribing the energy output to the actual nitration process. It was, therefore, decided to repeat the calorimetric measurement, but at a much reduced substrate loading (1.6 % as opposed to 16 % (m/v)).

The dilute p-cresol nitration was carried out on the reaction calorimeter as previously discussed. In this case, p-cresol (4.06 g; 37.5 mmol) and 250 cm³ 1,2-dichloroethane was placed in the reactor. 65 % Nitric acid (3.62 g; 37.7 mmol) was added to the reactor at a constant flow rate of 0.5 cm³.min⁻¹. The heat of reaction was monitored, and samples analysed by HPLC. The results of this reaction are given in Table 5.4, and the energy plot shown in Figure 5.5.

Table 5.4: Dilute calorimetric nitration of p-cresol

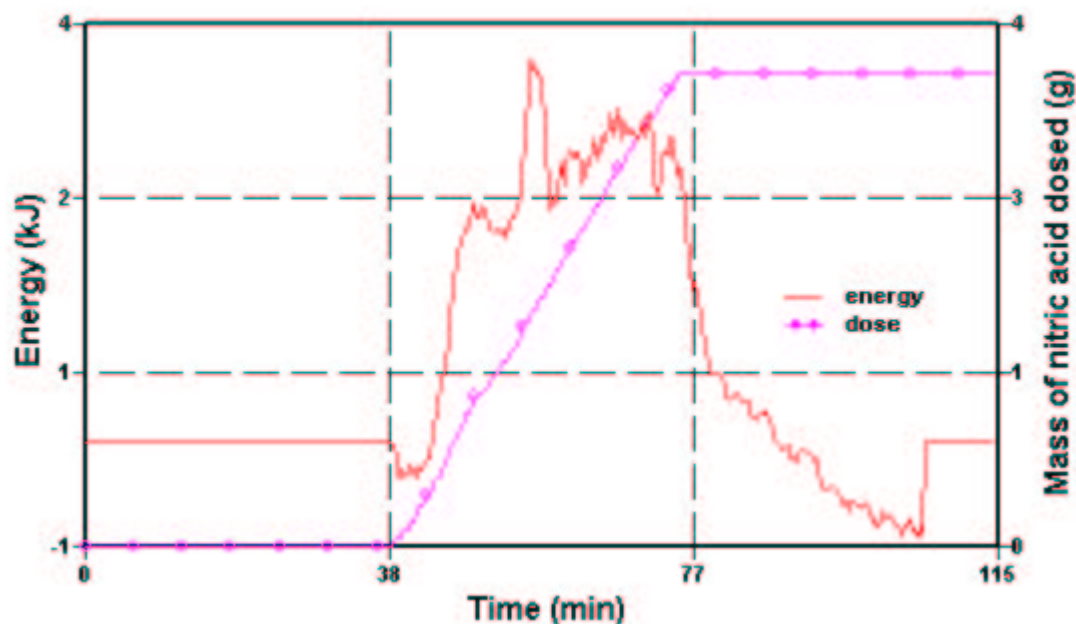
Substrate load (%)	Conv. (%)	Yield 2NPC (%)	Yield DNPC (%)	Account. (%)
1.6	100	91.3	3.4	95.5

A : S ratio – 1 : 0.987

2NPC: 4-methyl-2-nitrophenol

DNPC: 2,6-dinitro-p-cresol

Figure 5.5: Energy plot for the dilute calorimetric nitration of p-cresol



The yield of 2NPC (4-methyl-2-nitrophenol) and the accountability for this reaction were much higher than that observed for the reactions carried out with the higher substrate load (1.6 % versus 16 %). The results of this experiment

were comparable to those carried out on bench-scale. The calorimetry of this reaction was very similar to the previous reaction. An initial reaction exotherm is again observed, however not as pronounced as in the previous case. After this initial exotherm the power output remains more or less constant until dosing is completed and the reaction heat drops off completely.

The heat of reaction was found to be -119.67 kJ per mole, which is considerably higher than that obtained for the higher substrate loading (-103.67 kJ/mol). The difference is probably a reflection of the difference in the two types of reactions, nitration to the desired product and oxidation to form by-products.

5.3.3 Effect of catalyst on heat of reaction

The energy plots of the previous calorimetric experiments exhibited a very sharp initial reaction exotherm, and it was of interest to study the origin of this exotherm. No catalyst was used for the preceding calorimetric reactions, hence it was decided to investigate the effect of strong acids (nitration catalysts) on the reaction.

Three additional reactions were carried out, as described in § 5.3.1, with the exception that sulphuric acid or triflic acid (trifluoromethanesulphonic) was added to the reaction mixture. In the first reaction, 98 % sulphuric acid (1.24 g; 12.1 mmol) was added to the substrate/ solvent mixture, before addition of nitric acid was started. Sulphuric acid (1.29 g; 12.6 mmol) was also added to the second reaction, but in this case it was mixed with the 65 % nitric acid and dosed at a constant flow rate. The third reaction made use of triflic acid (1.86 g; 12.4 mmol), a well-known nitration catalyst of high acid strength,³⁰ which was added to the substrate/ solvent mixture. These reactions were compared to the calorimetric nitrations initially carried out. The results are summarised in Table 5.5, and a comparative energy plot is shown in Figure 5.6.

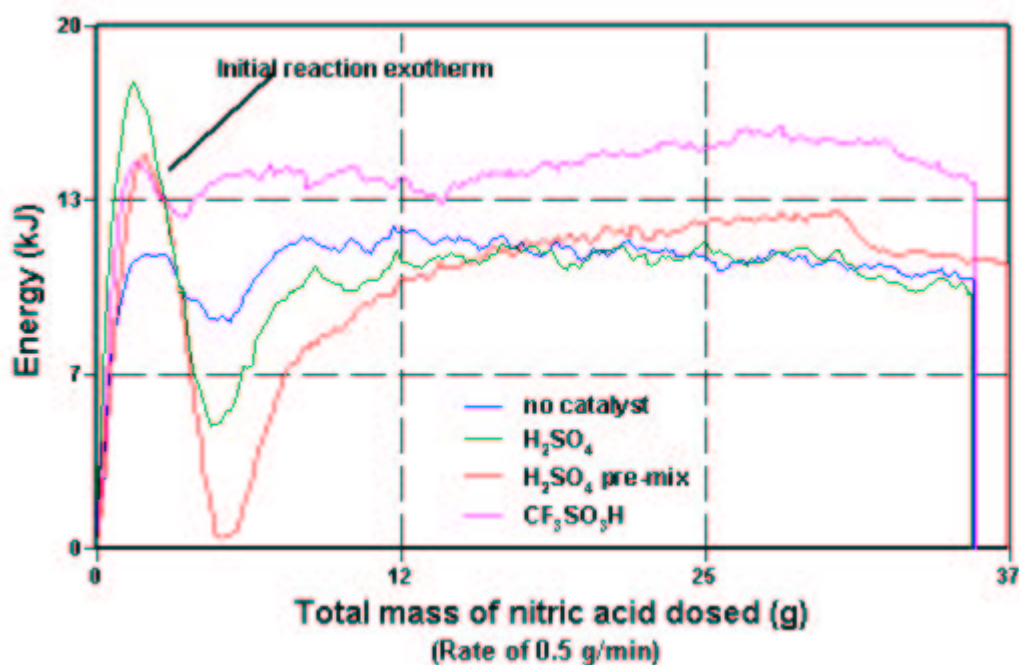
Table 5.5: Effect of a catalyst on the formation of products and heat of reaction

Catalyst	A : S	Conv. (%)	Yield 2NPC (%)	Account. (%)	ΔH_r (kJ/mol)
None	1 : 1.002	98.3	48.5	50.4	-103.67
H ₂ SO ₄	1 : 1.038	99.3	50.6	51.7	-83.09
H ₂ SO ₄ mixed	1 : 0.997	96.7	56.5	60.2	-80.94
CF ₃ SO ₃ H	1 : 1.008	99.1	55.4	56.7	-113.11

2NPC – 4-methyl-2-nitrophenol

All reactions – substrate load of 16 % (m/v)

Figure 5.6: Overlaid energy plots of various acids



From the above results, it can be seen that the yields and accountabilities obtained were all in the same range, however, the pre-mixed sulphuric acid-catalysed reaction provided the best results (accountability of 60 %). This reaction also gave the lowest ΔH_r . It is interesting to note the increase in the yield and accountability caused by mixing sulphuric acid with nitric acid prior to reaction. There was, however, little difference in the reaction heats between the two sulphuric acid-catalysed reactions. The triflic acid-catalysed reaction

produced the highest heat of reaction, which compares favourably with the energy obtained during the nitration when using a low substrate loading. Triflic acid is known to catalyse electrophilic aromatic substitution reactions, such as aromatic nitration. These results therefore seem to confirm previous suggestions that a higher reaction heat is associated with nitration as compared to oxidation. While sulphuric acid is known to be a strong oxidant and also to catalyse oxidation processes,⁷¹ triflic acid is not an oxidant.

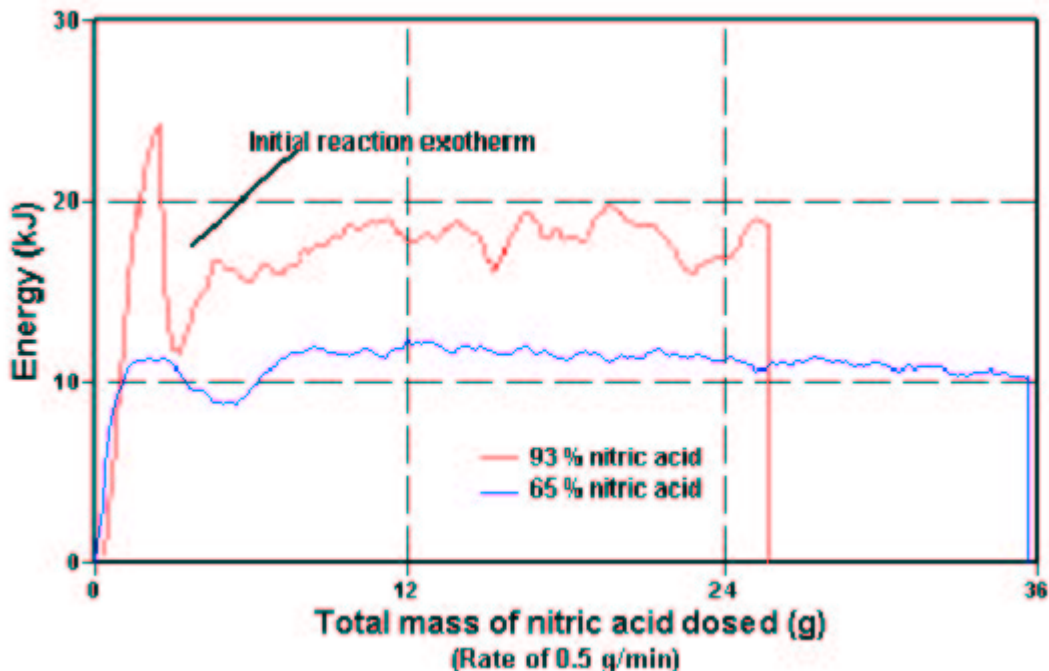
5.3.4 Effect of nitric acid concentration on the heat of reaction

In another calorimetry experiment, the concentration of nitric acid was increased to 93 %. It was also important to determine the effect that the acid concentration would have on the yield and accountability. p-Cresol (40.0 g; 370 mmol) was added to 250 cm³ 1,2-dichloroethane and placed in the reactor. Fuming nitric acid (25.6 g; 361 mmol) was dosed to the reactor at a constant rate of 0.5 g.min⁻¹ over approximately 51 minutes. HPLC analysis of reaction samples gave the results summarised in Table 5.6. The energy plots for the varying acid concentrations are compared by means of an overlay plot in Figure 5.7.

Table 5.6: Effect of acid concentration on the reaction results

[HNO₃] (%)	A : S	Conv. (%)	Yield 2NPC (%)	Account. (%)	ΔH_r (kJ/mol)
65	1 : 1.002	98.3	48.5	50.4	-103.67
93	1 : 1.025	96.7	70.3	76.9	-139.94

Figure 5.7: Overlaid energy plots of various nitric acid concentrations



Higher yields and accountabilities were obtained with the use of fuming nitric acid than in reactions where 65 % nitric acid was used when a substrate load of 16 % was used. The heat of reaction for the concentrated acid reaction was also much higher than when dilute nitric acid was used. The energy plot shows that the peak of the “initial reaction exotherm” was also much larger than for the 65 % nitric acid reaction. The drop in the reaction heat after the initial exotherm seems to be quite large at first, for the fuming nitric acid. However, these drops are in the same proportions to the initial peaks for both acids.

5.3.5 Estimation of the heat of reaction

Since reaction calorimetry is an experimental procedure, results obtained using this technique must be compared to some form of standard value. The technique is still relatively new and thus very little data have been collected from the use of this technique.

Enthalpies for certain compounds have been compiled for a number of years and may be found in reference works such as the Handbook of Chemistry and Physics (CRC).⁷² These tables are however very limited, with very little available

data on complicated molecules. It has thus necessitated the use of an estimation technique.⁷³

Heat of reaction (enthalpy) can be determined from the enthalpies of formation, ΔH_f , of the compounds taking part in the reaction. Thus, for the reaction shown in Equation 5.6, the reaction enthalpy H_r is given by Equation 5.7, with the general form shown in Equation 5.8:



$$\Delta H_r = \epsilon \Delta H_{fC} + \delta \Delta H_{fD} - \alpha \Delta H_{fA} - \beta \Delta H_{fB} \quad \text{Equation 5.7}$$

$$\Delta H_r = \sum v_i \Delta H_{fi} \quad \text{Equation 5.8}$$

where v_i is the stoichiometric coefficient of compound i (according to the rules of chemical thermodynamics, v_i is positive for products and negative for educts), and ΔH_{fi} the enthalpy of formation of compound i .

Chemical reactions can be considered as processes in which molecular bonds are broken and others are formed. The thermodynamic functions for a chemical reaction can therefore be considered as the sum of the contributions of those chemical bonds which were altered by the reaction. In a similar approach, the structural groups of the reacting molecules can be used as the basis for estimating thermodynamic reaction quantities, in particular those of organic substances. A number of these group contribution methods have been proposed

for the estimation of standard enthalpies, Gibbs formation energies and standard entropies.

In the Joback⁷³ method, ΔH_{f298}° is calculated according to Equation 5.9:

$$\Delta H_{f298}^{\circ} = 68.29 + \sum s_i I_{Hi} \quad \text{Equation 5.9}$$

where s_i is the number of structural groups of type I and I_{Hi} are the increments of structural groups I for the enthalpy of formation. It is evident from the above equation that the enthalpy of formation can only be directly calculated for a temperature of 298.15 K. In order to calculate these quantities for other temperatures, the molar heat capacities, c_p° , have to be evaluated as a function of temperature by means of Equation 5.10.

$$\Delta H_{rT}^{\circ} = \Delta H_{r298}^{\circ} + \int_{298.15}^T \Delta c_{pr}^{\circ} dT \quad \text{Equation 5.10}$$

Deviations of standard enthalpies of formation and Gibbs energies calculated using this method are mostly below 10 kJ/mol, but a number of cases have been found where large differences were observed. With methods such as the one proposed by Benson,^{74,75} errors are somewhat smaller because it allows larger structural differentiation. These methods are however rather tedious in their application and will not be further discussed.

By making use of Equation 5.9, the enthalpies of formation for p-cresol and 4-methyl-2-nitrophenol were estimated using Joback's increments, and found to be -128.59 and -150.82, respectively. Joback's increments are shown in Table 5.7. The heats of formation of aqueous nitric acid and water were found in the CRC.⁷² Equation 5.8 was then used to calculate the heat of reaction (298 K) of the nitration of p-cresol. This value was found to be -100.75 kJ/mol, but could,

however, not be directly compared with the experimentally determined value since the reactions were carried out at 50°C. The estimated heat of reaction, at 298 K, thus had to be evaluated at 323 K. Equation 5.10 was used to calculate ΔH_{rT}° at 50°C, but first the Δc_{pr}° had to be determined. This is essentially a heat balance of the heat capacities of the species taking part in the reaction, and may be calculated using Equation 5.11.

$$\Delta c_{pr} = \sum v_i c_{pi} \quad \text{Equation 5.11}$$

The same problem was experienced with the availability of heat capacity data, as was experienced with the formation enthalpies of nitroresol etc. This value had to be estimated, and use was made of Joback's group contribution method for the estimation of calorific properties.⁷³ This necessitated the use of Equation 5.12:

$$c_p^{\circ} = \left(\sum s_j I_a - 37.93 \right) + \left(\sum s_j I_b + 0.210 \right) T + \left(\sum s_j I_c + 3.91 \times 10^{-4} \right) T^2 + \left(\sum s_j I_d + 2.06 \times 10^{-7} \right) T^3 \quad \text{Equation 5.12}$$

where s_j is the number of the group j and the increments I_a , I_b , I_c and I_d , are component-specific parameters and are tabulated for various groups. The average error in c_p° is usually less than 2 %.⁷³ Table 5.7 gives the Joback increments used for this calculation.

Table 5.7: Joback's increments for the estimation of ΔH_r and c_p°

Group	$s_{i,j}$	I_H	I_a	I_b	I_c	I_d
non ring						
-CH ₃	1	-76.45	19.5	-8.08×10^{-3}	1.53×10^{-4}	-9.67×10^{-8}

ring						
=CH–	3	2.09	-2.14	5.74×10^{-2}	-1.64×10^{-6}	-1.59×10^{-8}
=C<	3	46.43	-8.25	0.101	-1.42×10^{-4}	6.78×10^{-8}
oxygen						
–OH (phenol)	1	-221.65	-2.81	0.111	-1.16×10^{-4}	4.94×10^{-8}
nitrogen						
–NO ₂	1	-66.57	25.9	-3.74×10^{-3}	1.29×10^{-4}	-8.88×10^{-8}

The values for c_{p298}° and Δc_{pr}° were found to be $154.96 \text{ J}\cdot\text{mol}^{-1}\cdot\text{K}^{-1}$ and $-30.21 \text{ J}\cdot\text{mol}^{-1}\cdot\text{K}^{-1}$, respectively. ΔH_{r323} , calculated according to Equation 5.10, was found to be -101.51 kJ/mol .

This final result compared very well with the experimental values obtained on the reaction calorimeter. It should, however, be noted that the values obtained by calorimetry consist of a combination of reaction heats, whereas the calculated heats are for the nitration reaction only.

5.4 CONCLUDING REMARKS

- In the first calorimetric nitration, an isolated yield of 45.9 % was obtained. A heat of reaction of -103.67 kJ/mol was obtained for the nitration of p-cresol with 65 % nitric acid in a 1 : 1 acid to substrate ratio, in the absence of catalyst, with 1,2-dichloroethane as solvent.
- The reaction was repeated on the calorimeter, this time with sampling to facilitate the construction of a product distribution diagram. The product distribution showed that the accountability was approximately 50 %. The reaction mass was collected and the waste separated from the product. The waste was dried and weighed and the mass added to the mass of product (calculated from the analytical yield). This increased the accountability of the reaction to 94.5 % of the theoretical yield. The side products were identified

by GC-MS analysis and found to consist of dimers of p-cresol and nitro-p-cresol.

- The calorimetry was repeated with the substrate load of only 10 % of the previous scaled-up reactions (1.6 % substrate load). Analysis of this mixture showed an increase in the yield of 2NPC and the accountability to 91.3 and 95.5 %, respectively. The decreased substrate load was thus responsible for an associated increase in both yield and accountability. The heat of reaction was much higher for this reaction, but this could be attributed to the volume differences as well as the composition of the reaction mixture and thus its heat characteristics.
- Sulphuric acid or triflic acid was added to the reaction mixture to ascertain its the effect on a region of the energy plot, called the “initial reaction exotherm”. ΔH_r values for sulphuric acid were much lower than those of triflic acid and neat reaction mixtures. Triflic acid had the highest heat of reaction (approximately -114 kJ/mol). The energy plot showed a very different profile for triflic acid; very little NO_2 gas was evolved in this reaction. All these factors seem to indicate that an alternative mechanism was operative in the presence of triflic acid. When sulphuric acid was pre-mixed with nitric acid, the lowest ΔH_r was obtained while it gave the highest yield and accountability. Again the material balance was very low when a substrate load of 16 % was used.
- A reaction was carried out with 93 % nitric acid and no catalyst to determine the effect on the accountability and product yield. The heat of reaction in this case was found to be -139.94 kJ/mol. The yield of 2NPC and accountability were found to be 70.3 and 76.9 %, respectively.
- The heat of reaction for the nitration of p-cresol at 50°C was determined by estimating the formation enthalpy and molar heat capacity of 4-methyl-2-nitrophenol. These values were found to be -150.82 kJ/mol and 154.96 $\text{J}\cdot\text{mol}^{-1}\cdot\text{K}^{-1}$. Integration of the change in heat capacity with respect to

temperature gave the heat of reaction for the nitration of p-cresol of -101.51 kJ/mol. This result was in agreement with experimental values. However, this value can only be estimated for the nitration process alone, and does not give any information concerning the p-cresol oxidation.

CHAPTER 6

SUMMARY AND CONCLUDING REMARKS

The nitration of m- and p-cresol under mild reaction conditions was investigated by means of the following steps, namely the:

Evaluation or development of nitration methods having a favourable influence on the regio-selectivity in the nitration of m-cresol, with the goal being the achievement of high ratios of para- to ortho-products.

Successful application of said methods to the nitration of p-cresol, with eventual scale-up of the reaction system and assessment of certain process efficiency criteria.

Application of calorimetry for the evaluation of the heat of nitration of p-cresol and the effect of certain reaction parameters on the heat evolved.

6.1 NITRATION OF m-CRESOL

- Yttrium(III)triflate was used as catalyst in the nitration of m-cresol at mild to low nitric acid concentrations at temperatures between 0 and 60°C. It was shown that $Y(TFA)_3$ catalysed the reaction, giving good yields and accountabilities; however, little difference was observed in the isomer distribution.
- Use was made of an experimental design to evaluate reaction parameters such as reaction temperature, acid concentration and the acid to substrate ratio. It was found that the A : S ratio was significant for all of the design responses. The derived model indicated that decreased temperatures and acid concentrations did increase the selectivity to 4NMC and the overall accountability.

- The use of metal supported clays as nitrating agents as well as the use of a mixture of nitric and sulphuric acid was applied to the nitration of m-cresol. Of the various methods, only the mixed acid system gave results comparable to those obtained in dichloroethane with dilute nitric acid. This method gave a high apparent preference for 4NMC, with almost a complete absence of the formation of 2-methyl-1,4-benzoquinone.
- A different mechanism to that reported was proposed for the nitration of activated aromatic substrates with dilute acid, which could better account for the formation of 2-methyl-1,4-benzoquinone. This mechanism is thought to proceed via nitrosation, formation of the monoxime and subsequent hydrolysis to the benzoquinone.
- Nitration via nitrosation is known to have a high preference for para-substitution. However, this procedure could not be successfully applied (in terms of conversions and yields), while a high p : o ratio was obtained.

6.2 NITRATION OF p-CRESOL

- p-Cresol was nitrated in 1,2-dichloroethane and iso-propanol with mild and high acid concentrations (65 and 93 %, respectively). Reactions in dichloroethane generally gave high yields and accountabilities. Reactions with high acid concentrations gave a higher proportion of dinitrated products.
- Substrate loading was found to be the single most important factor, influencing the yield of 2NPC and the accountability significantly. By carefully controlling the A : S ratio, together with high stirring rates and slow addition rates, the formation of products could be controlled.

- Side products were identified by GC-MS and proposed to be the result of the oxidation of p-cresol to form the quinomethide intermediate which then reacted with substrate or product.
- Scale-up of the reaction showed that the isolation method was relatively successful as a means of separating and purifying the product (2NPC). A mass balance was carried out on one of the reactions. Some material losses did occur; however, the total process accountability was acceptable.

6.3 HEAT OF p-CRESOL NITRATION

- Calorimetry was used to evaluate the heat evolved during the nitration reaction. Nitration of p-cresol in dichloroethane with 65 % nitric acid was found to be a highly exothermic process with heat of -103.67 kJ/mol being released.
- Waste generated by the scaled-up nitration process was isolated and added to the product yield. This increased the reaction accountability significantly and was in good agreement with the trends observed from the product distribution diagram.
- Substrate loading was found to also have an impact on the heat evolved during the nitration process.
- Nitration with sulphuric acid as catalyst gave a heat of reaction much lower than that obtained in neat nitration mixtures. Triflic acid gave the highest heat of reaction. This was attributed to the fact that sulphuric acid also promoted oxidation processes which released less heat. Triflic acid catalyses nitration only, releasing more heat than neat reaction mixtures.

- The heat of reaction for the nitration of p-cresol was estimated, and this value was found to compare well with those experimentally obtained. These theoretical values, however, only describe the nitration process whereas the experimentally obtained values were also influenced by side reactions, such as the proposed oxidation process.

This work has shown that the direct nitration of cresol may successfully be carried out with dilute nitric acid in the absence of any catalyst. The manipulation of reaction variables to increase the p : o ratio was, however, not as easily carried out. However, until nitrosation can effectively be applied to m-cresol, high p : o ratios will remain the "Holy Grail" of the nitration of highly activated substrates. Results from this work have however helped to shed some light on the mechanism for the formation of the benzoquinone species. The substrate loading was found to be extremely important in nitration of activated aromatic substrates. Furthermore, nitration is an extremely exothermic process which, together with the previously mentioned fact, has serious implications on the application of this reaction on production scale

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REFERENCES

- 1) G. C. Gerrans, "South Africa – History of the chemical industry introduction", <http://mbendi.co.za/caia/chsahs01.htm> and all internet links found at this website.
- 2) "Sasol announces R835-million n-butanol plant and plans for acrylic acid in South Africa" and "New detergent alcohol plant for SASOL", http://mbendi.co.za/a_sndmsg/news_view.asp.
- 3) B. Anderson, "Dow Chemical on lookout for further SA investment", <http://www.businessday.co.za/b.day/index/direct/1,3524,6128-2,00.html>.
- 4) J. Meintjies, *Sasol 1950 - 1975*, Tafelberg-Uitgewers Beperk, Capetown, (163pp.), (1975).
- 5) B.H. Weil, J.C. Lane, *The Technology of the Fischer-Tropsch Process*, London Constable & Co Ltd., London, pp. 6 - 23, (1949).
- 6) P. Tooley, *Fuels, Explosives and Dyestuffs – Today*, John Murray, London, pp. 103 - 160, (1971).
- 7) H.A. Wittcoff, B.G. Reuben, *Industrial Organic Chemicals in Perspective, Part One: Raw Materials and Manufacture*, John Wiley and Sons, New York, pp. 39 - 45 and pp. 127 - 131, (1980).
- 8) G.A. Cook, *Survey of Modern Industrial Chemistry*, Ann Arbor Science Publishers, Michigan, pp. 147 - 178, (1980).
- 9) H. Fiege, "Cresols and xylenols" in: *Ullman's Encyclopedia of Industrial Chemistry*, W. Gerhartz and Y.S. Yamamoto (Eds.), 5th ed., VCH, New York, Vol. **A8**, pp. 25 – 59, (1991).
- 10) G. Booth, "Nitro compounds, aromatic" in: *Ullmann's Encyclopedia of Industrial Chemistry*, W. Gerhartz and Y.S. Yamamoto (Eds.), 5th ed., VCH, New York, Vol. **A17**, pp. 411 – 455, (1991).
- 11) J. Buckingham, S.M. Donaghy, *Dictionary of Organic Compounds*, 5th ed., Vol. **4**, Chapman and Hall, pp. 3831 – 3832 and pp. 3951 – 3952, (1982).
- 12) B. Hilleman, "Pesticides triggers large-scale evacuation, decontamination effort", *Chemical and Engineering News*, Vol. **74**, (51), 22 – 23, (1996).

- 13) B. Hilleman, "Methyl parathion: EPA's challenge", *Chemical and Engineering News*, Vol. **75**, (4), 28, (1997).
- 14) J. March, *Advanced Organic Chemistry- Reactions, Mechanisms and Structures*, 4th ed., John Wiley and Sons, New York, pp. 501 – 525 and 884 – 885, (1992).
- 15) G.A. Olah, "Mechanism of electrophilic aromatic substitution", *Accounts of Chem. Res.*, Vol. **4**, 240 – 248, (1971).
- 16) J.H. Ridd, "Mechanism of aromatic nitration", *Accounts of Chem. Res.*, Vol. **4**, 248 – 253, (1971).
- 17) P. Sykes, *A Guidebook to Mechanism in Organic Chemistry*, 6th ed., Longman Scientific & Technical, London, pp. 130 – 177, (1986).
- 18) E. S. Gould, *Mechanism and Structure in Organic Chemistry*, Holt Rinehart & Winston Inc., London, pp. 419 – 440, (1969).
- 19) R. J. Qualette, J.D. Rawn, *Organic Chemistry*, J. Challice and P.F. Corey (Eds.), Prentice Hall Inc., New Jersey pp. 506 – 520, (1996).
- 20) T.W.G. Solomons, *Organic Chemistry*, 5th edition, John Wiley & Sons Inc., New York, pp. 654 – 664, (1992).
- 21) L. Delaude, P. Laszlo, K. Smith, "Heightened selectivity in aromatic nitrations and chlorinations by the use of solid supports as catalysts", *Accounts of Chem. Res.*, Vol. **26**, 607 – 613, (1993).
- 22) D. W. Amos, D. A. Baines, G. W. Flewett, "Nitration of titanium(IV)nitrate", *Tetrahedron Letters*, Vol. **34**, 3191 – 3194, (1973).
- 23) A. Cornelius, P. Laszlo, "Clay- supported copper(II) and iron(III) nitrates: novel multi- purpose reagents for Organic synthesis", *Synthesis*, October, 909 – 918, (1985).
- 24) A. Cornelius, P. Laszlo, P. Pennetreau, "Nitration of estrone into 2-nitroestrone by clay-supported ferric nitrate", *J. Org. Chem.*, Vol. **48**, 4771 – 4772, (1983).
- 25) B. Gigante, A. O. Prazeres, M. J. Marcelo-Curto, A. Cornelius, P. Laszlo, "Mild and selective nitration by 'claycop'", *J. Org. Chem.*, Vol. **60**, 3445 – 3447, (1995).

- 26) F. J. Waller, A. G. Barret, D. C. Braddock, D. Ramprasad, "Lanthanide(III)triflates as recyclable catalysts for atom economic aromatic nitration", *Chem. Commun.*, Vol. **6**, 613 – 614, (1997).
- 27) A. Kawada, S. Mitamura, S. Kobayashi, "Ln(Otf)₃ – LiClO₄ as reusable catalyst system for Friedel-Crafts acylation", *Chem. Commun.*, 183 – 184, (1996).
- 28) A. Kawada, S. Mitamura, S. Kobayashi, "Lanthanide Trifluoromethanesulphonates as reusable catalysts: catalytic Friedel-Crafts acylation", *J. Chem. Soc., Chem. Commun.*, 1157 – 1158, (1993).
- 29) S. Kobayashi, I. Hachiya, "Lanthanide triflates as water- tolerant Lewis acids. Activation of commercial formaldehyde solution and use in Aldol reaction of silyl enol ethers with aldehyde in aqueous media", *J. Org. Chem.*, Vol. **59**, 3590 – 3596, (1994).
- 30) C. L. Coon, W.G. Blucher, M.E. Hill, "The nitration with nitric acid and trifluoromethanesulphonic acid", *J. Org. Chem.*, Vol. **38**, (25), 4243 – 4248, (1973).
- 31) B. A. Kowalczyk, P. N. Roberts, G. K. McEwan, J. Robinson, "Scale up of the nitration of 1-acetyl-3,4-dichloro-1,2-(ethylenedioxy)benzene using nitric acid/ trifluoroacetic acid", *Organic Process Research and Development*, Vol. **1**, 355 – 358, (1997).
- 32) R. G. Coombes, J. G. Golding, G. D. Tobin, J. W. Barnett, R. B. Moodie, K. Schofield, J. B. Weston, "Electrophilic aromatic substitution. Part 16. The nitration of anisole, o-methylanisole and p-methylanisole in aqueous sulphuric acid", *J. C. S. Perkin II*, 248 – 255, (1977).
- 33) R. G. Coombes, J. G. Golding, P. Hadjigeorgiou, "Electrophilic aromatic substitution. Part 23. The nitration of phenol and the cresols in aqueous sulphuric acid", *J. C. S. Perkin II*, 1451 – 1459, (1979).
- 34) M. Sasaki, K. Mukai, "Preparation of 5-methyl-2-nitrophenol", US Patent No. 4 034 050, (1977).
- 35) H. Kanno, H. Chida, Y. Otani, "Selective nitration of phenol derivatives", US Patent No. 5 847 231, (1998).
- 36) L. A. Subluskey, "Manufacture of para-nitro-meta-cresol from meta/ para-cresol mixtures" US Patent No. 3 980 717, (1976).

- 37) H. B. Kagan, P. Gigard, M. Quertani, "Selective nitration of phenols catalysed by lanthanum(III)nitrate", *Tetrahedron Letters*, Vol. **23**, (42), 4315 – 4318, (1982).
- 38) M. J. Thompson, P. J. Zeegers, "Studies on the two-phase nitration of selected phenols", *Tetrahedron Letters*, Vol. **29**, (20), 2471 – 2474, (1988).
- 39) D. S. Ross, G. P. Hum, W.G. Blucher, "Catalysis of aromatic nitration by the lower oxides of nitrogen", *J. Chem. Soc., Chem. Commun.*, 532 – 533, (1980).
- 40) K. Schofield, R. B. Moodie, J. G. Hoggett, "The duality of mechanism for nitration in acetic anhydride", *J. Chem. Soc., Chem. Commun.*, 605 – 606, (1969).
- 41) A. Fischer, G. N. Henderson, "Ipso nitration: nitration of 2-alkylphenols in acetic anhydride. Formation of 6-alkyl-6-nitrocyclohexa-2,4-dienones", *Tetrahedron Letters*, Vol. **21**, 4661 – 4662, (1980).
- 42) T. McCullough, "Beauty or the beast: nitration of phenol", *J. Chem. Ed.*, Vol. **67**, (9), 801, (1990).
- 43) I. J. G. Priestley, J. P. Muxworthy, J. H. Atherton, M. Lennon, S. M. Brown, "Nitration process", US Patent No. 5 952 531, (1999).
- 44) A. Germain, "Solvent effects in the two-phase nitration of anisole", *J. Chem. Soc., Chem. Commun.*, 1697 – 1698, (1990).
- 45) G. A. Olah, S. C. Narang, J. A. Olah, R. L. Pearson, C. A. Cupas, "Aromatic substitution 45. Transfer Nitrations of aromatics with *N*-nitropyridinium and quinolinium ions", *J. Am. Chem. Soc.*, Vol. **102**, (10), 3507 – 3510, (1980).
- 46) J. K. Kochi, E. K. Kim, K. Y. Lee, "Aromatic nitration with electrophilic *N*-nitropyridinium cations. Transitory charge-transfer complexes as key intermediates", *J. Am. Chem. Soc.*, Vol. **114**, 1756 – 1770, (1992).
- 47) H. Pervez, L. Rees, C. J. Suckling, "Selective nitration of phenol", *J. Chem. Soc., Chem. Commun.*, 512 – 513, (1985).
- 48) E. Santaniello, M. Ravasi, P. Ferraboschi, "A-Ring nitration of estrone", *J. Org. Chem.*, Vol. **48**, 739 – 740, (1983).

- 49) A. Fischer, N. Mathivanan, "Formation of dienones on the reaction of cresols, xylenols and 2-naphtol with nitrogen dioxide: observation of keto tautomers of nitrophenols", *Tetrahedron Letters*, Vol. **29**, (16), 1869 – 1872, (1988).
- 50) R. G. Coombes, A. W. Diggle, S. P. Kempsall, "The mechanism of phenol and 4-methylphenol by nitrogen dioxide in solution", *Tetrahedron Letters*, Vol. **35**, (34), 6373 – 6376, (1994).
- 51) M. Attina, F. Cacace, "Substrate and positional selectivity of the gas-phase nitration of substituted benzenes by protonated methyl nitrate. The first example of a well-behaved aromatic nitration by a gaseous cation", *J. Am. Chem. Soc.*, Vol. **108**, 318 – 319, (1986).
- 52) J. H. Ridd, S. Dintürk, "Reactions of cerium(IV) ammonium nitrate with aromatic compounds in acetonitrile. Part 1. The mechanism of side-chain substitution", *J. C. S. Perkin II*, 961 – 964, (1982).
- 53) I. Keeley, "The evaluation of technical production processes for 2-chloro-3-phenoxy-6-nitroaniline", M. Tech.: Chemistry Dissertation, P.E. Technikon, (1999).
- 54) J. R. Chapman, *Practical Organic Mass Spectrometry*, 2nd ed., John Wiley and Sons, New York (330pp.), (1993).
- 55) W. Kemp, *Organic Spectroscopy*, 3rd ed., Macmillan Press Ltd., London, (392pp.), (1991).
- 56) G. E. P. Box, K.B. Wilson, *J. Roy. Statist. Soc.*, Vol. **B13**, 1, (1951).
- 57) G. E. P. Box, J. S. Hunter, *Ann. Math. Statist.* Vol. **28**, 195, (1957).
- 58) R. Carlson, Data handling in science and technology 8: Design and optimization in organic synthesis, Elsevier, Amsterdam, 201-205, (1992).
- 59) R. H. Meyers, D. C. Montgomery, *Response Surface Methodology*, V. Banet and R. A. Bradley (Eds.), John Wiley and Sons, New York, (700pp.), (1995).
- 60) L. Davies, *Efficiency in Research, Development and Production: The Statistical Design and Analysis of Chemical Experiments*, The Royal Society of Chemistry, Cambridge, (179pp.), (1993).

- 61) E. Fache, D. Laucher, M. Constantini, M. Beclere, F. Perrin-Janet, "The roots of organic development", in: *Industrial Chemistry Library*, J. Desmurs and S. Ratton (Eds.), Elsevier, Amsterdam, Vol. **8**, pp. 368 – 379, (1996).
- 62) H. Beyer, W. Walter, *Handbook of Organic Chemistry*, Prentice Hall Inc., New Jersey, pp. 516, (1996).
- 63) W. E. Smith, T. W. McGee, "Nitrosation of aromatic compounds", US Patent no. 4232175, (1980).
- 64) B. M. Schoonees, "The production of hydroxy-substituted aromatic aldehydes and ketones by catalytic, liquid-phase oxidation" D. Tech.: Chemistry Thesis, P.E. Technikon, (2000).
- 65) R. A. Sheldon, N. de Heij, "Aromatic aldehydes via catalytic oxidation" in: *Role of Oxygen in Chemistry and Biochemistry*, W. Ando and Y. Moro-oka (Eds.), Elsevier, Amsterdam, pp. 243 – 258, (1988).
- 66) Hammerich, Svensmark, "Oxygen-containing compounds" in: *Organic Electrochemistry – an Introduction and a Guide*, H. Lund and M.M. Baizer, 3rd ed., Marcel Dekker, New York, pp. 616 – 628, (1991).
- 67) J. Singh, "Reaction calorimetry for process development: recent advances", *Process Safety Progress*, Vol. **16**, 43 – 49, (1997).
- 68) J. Singh, "Automation of reaction research- an alternative to robotics", *Hazard Evaluation Laboratory – Products and Services catalogue*, 157 – 160.
- 69) J. Singh, "Batch runaway relief: re-evaluation of "credible" scenario", *Process Safety Progress*, Vol. **16**, 255 – 261, (1997).
- 70) "Non isothermal calorimetry", Hazard Evaluation Laboratory – *Similar Operating Manual*, 1 – 20.
- 71) T.L. Brown, H.E. LeMay, B.E. Bursten, *Chemistry – The Central Science*, 5th ed., Prentice Hall Inc., New Jersey, pp. 841, (1991).
- 72) *CRC Handbook of Chemistry and Physics*, D.R. Lide and H.P.R. Friederikse (Eds.), 74th ed., CRC Press Inc., pp. 5-1 – 5-75, (1993).
- 73) O. Ulfert, P. Hanns-Ingolf, "Estimation of physical properties" in: *Ullmann's Encyclopedia of Industrial Chemistry*, W. Gerhartz and Y.S. Yamamoto (Eds.), 5th ed., VCH, New York, Vol. **B1**, chapter 6, pp 1 – 55, (1991).

- 74) S. W. Benson, F. R. Cruickshank, D. M. Golden, G. R. Haugen, H. E. O'Neal, A. S. Rodgers, R. Shaw, R. Walsh, "Additivity rules for the estimation of thermochemical properties", *Chemical Reviews*, Vol. **69**, 279 Amsterdam: 324, (1969).
- 75) S.W. Benson, "Methods for the estimation of thermochemical data" in *Thermochemical Kinetics*, 2nd ed., John Wiley and Sons, New York, pp. 19 – 72, (1976).

APPENDICES

3.1 MULTIPLE LEAST SQUARES CALCULATION OF THE FITTED RESPONSE SURFACE

Matrix algebra was used to calculate the individual model parameters. A model matrix, X , was first constructed by augmenting the design matrix with a column, 1, for the constant term β_0 . Columns for all the interaction terms, as well as columns for all the squared terms were included in the matrix.

The overall matrix calculation may be summarised by the matrix equation, Equation (I).

$$\mathbf{y} = \mathbf{X}\boldsymbol{\beta} + \mathbf{e} \quad \text{Equation (I)}$$

where y = the column vector of the experimental responses obtained, X = the model matrix, β = the column vector of the model parameters, and e = the column vector of the error terms associated with each model parameter.

A least squares fit was performed on the data by using Equation (II).

$$(\mathbf{X}^t\mathbf{X})^{-1}\mathbf{X}^t\mathbf{y} = \mathbf{b} \quad \text{Equation (II)}$$

where b = coefficient.

3.2 CALCULATIONS FOR ANOVA

3.2.1 Estimation of “Pure Error”

To obtain an independent estimate of the pure experimental error, six replicate experiments were carried out at the design centre (all variables fixed at their centre point values). The variable settings and responses obtained for these replicate runs are shown in Table 3.4. The mean error square is defined as:

$$s_1^2 = \frac{\sum (y_{0i} - \bar{y}_i)^2}{N_0 - 1} \quad \text{Equation (III)}$$

Using the responses in Table 3.4, variances for conversion, yield, accountability and yield of 4NMC were found to be 0.00, 0.75, 0.69 and 0.16, respectively.

3.2.2 Significance of individual model parameters

The sum of squares (SS) for the individual, main and interaction effects was calculated using Equations (IV) and (V), respectively.

$$SS = \frac{(\sum a_i Y_i)^2}{N} \quad \text{Equation (IV)}$$

$$SS = \frac{(\sum a_i b_i Y_i)^2}{N} \quad \text{Equation (V)}$$

where a_i and b_i are the coded values for the respective factors in the i^{th} experimental run, Y is the observed experimental response in the i^{th} experimental run, and N is the number of experimental runs.

Since eight factorial experiments were used to estimate eight parameters (one average, three main effects, three 2-factor interactions and one 3-factor interaction), each effect was estimated with only one degree of freedom. The mean sum of squares (MSS) of the individual model parameters, defined as

SS/ d.o.f. (d.o.f. = degrees of freedom), was therefore the same as the individual sum of squares. To determine whether the contribution from the individual model terms was above the noise level given by the experimental error (s_{i^2}), an F-ratio was calculated (Equation (VI)) and compared to standard F-ratios.

$$F_{(u,v)} = \frac{MSS}{s_{i^2}} \quad \text{Equation (VI)}$$

where u = the number of degrees of freedom associated with MSS , and v = the number of degrees of freedom associated with s_{i^2} , the values being 1 and 5, respectively. This gave $F_{(1,5)} = 6.61$ at a 95 % confidence level.

3.2.3 Validation of the response surface model

To determine whether the experimentally-derived response surface model accurately described the response surface, several tests were performed to validate the model. The first of these was the lack-of-fit test. From the replicate experiments at the design centre, an estimate of the experimental error, s_1^2 , with $(N_0 - 1)$ degrees of freedom (N_0 = the number of centre point experiments), was calculated as described previously.

If the response surface model is a good approximation of the unknown response function, then the residuals should depend only upon the experimental error.

$$e = R_i^{obs} - R_i^{pred} \quad \text{Equation (VII)}$$

where R_i^{obs} and R_i^{pred} are the observed and predicted responses in the i^{th} experimental run respectively.

Each of the experiments in the series of N experiments ($N = N_a + N_c + N_0$; where N_a = the number of factorial experiments, N_c = number of star points and N_0 = number of centre points) were used to calculate a predicted experimental value by substituting the values of x_i for each experiment in the design matrix, into the

fitted model equation. The sum of the squared residuals was determined by the difference between the actual and predicted responses, and divided into two parts, one due to lack-of-fit, and the other due to pure error.

$$\sum e_i^2 = \text{RSS}(\text{lack of fit}) + \text{RSS}(\text{pure error}) \quad \text{Equation (VIII)}$$

The residual sum of squares due to lack-of-fit was obtained simply by subtracting the sum of squared deviations for the centre point experiments from the total residual sum of squares. The residual sum of squares, divided by the degrees of freedom, is the same variance as calculated previously (s_1^2). A second estimate of the experimental error variance, s_2^2 , was calculated using Equation (IX).

$$s_2^2 = \frac{\text{RSS}(\text{lack of fit})}{(\mathbf{N} - \mathbf{P}) - (\mathbf{N}_0 - 1)} \quad \text{Equation (IX)}$$

where N is the total number of experiments performed ($N_a + N_c + N_0$), P is the number of parameters in the response surface model, and N_0 is the number of experiments at the design centre.

The estimates of s_1^2 and s_2^2 were obtained with 5 and 5 degrees of freedom, respectively. To check whether these values were significantly different, an F-test was used (Equation (X)).

$$\mathbf{F} = s_1^2 / s_2^2 \quad \text{Equation (X)}$$

These values were all higher than the critical F-value ($F_{5, 5} = 5.05$) at a 95 % confidence level. This fact then indicated that the model did not give a good description of the response surface (described in detail in § 3.3.3.5).

The corrected total sum of squares (SST) and the corrected sum of squares of residuals (SSR) may be respectively calculated with Equations (XI) and (XII).

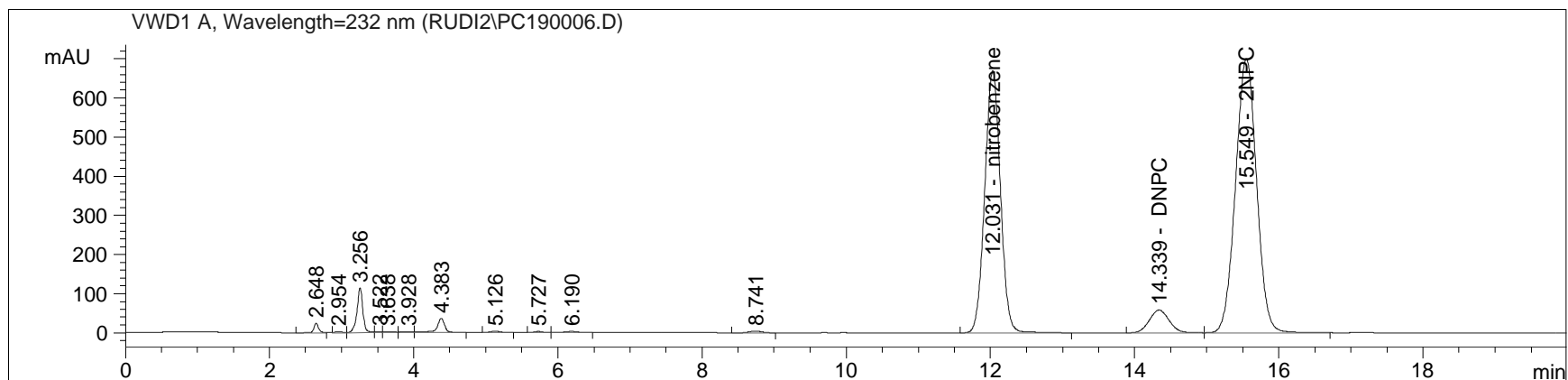
$$\mathbf{SST} = \sum (\mathbf{R}^2) - \frac{(\sum \mathbf{R})^2}{\mathbf{N}} \quad \mathbf{Equation (XI)}$$

$$\mathbf{SSR} = \sum (\mathbf{R}_{\text{pred}}^2) - \frac{(\sum \mathbf{R}_{\text{pred}})^2}{\mathbf{N}} \quad \mathbf{Equation (XII)}$$

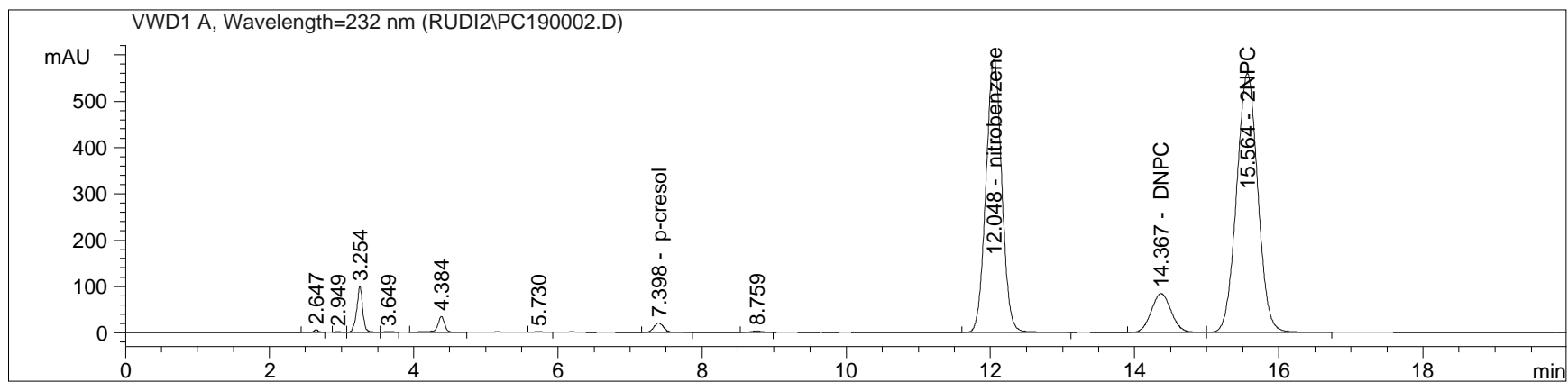
were \mathbf{R} = design responses and \mathbf{R}_{pred} = the predicted design responses.

4.1 HPLC chromatograms showing unidentified peaks in the nitration of p-cresol

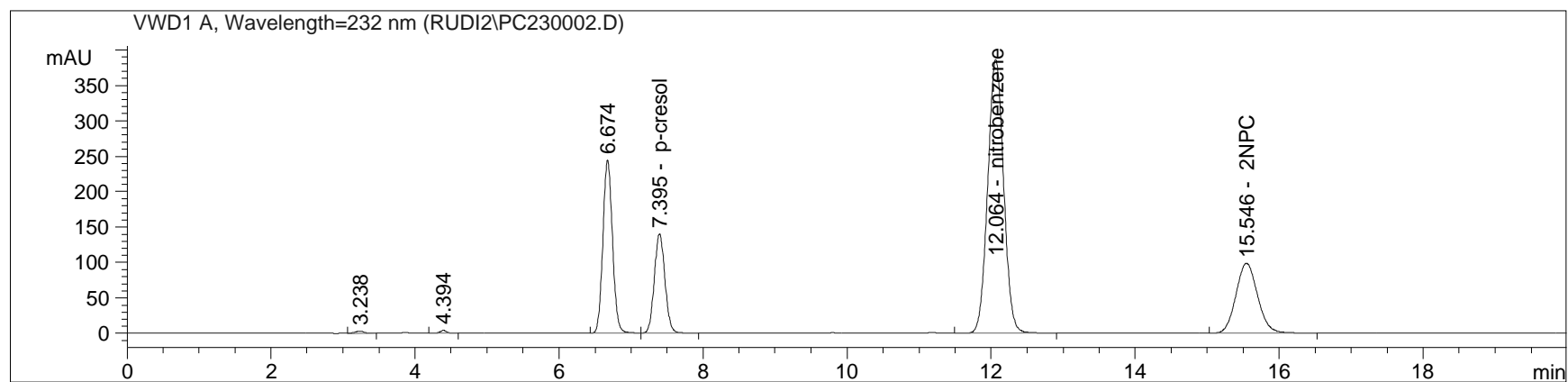
a)



b)

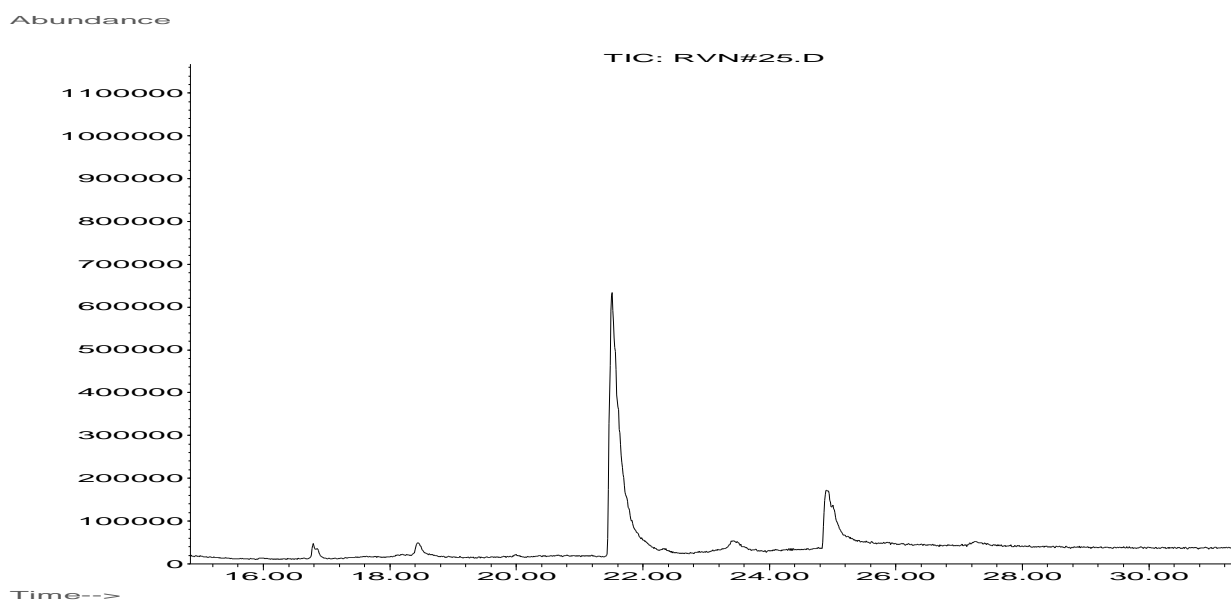


c)

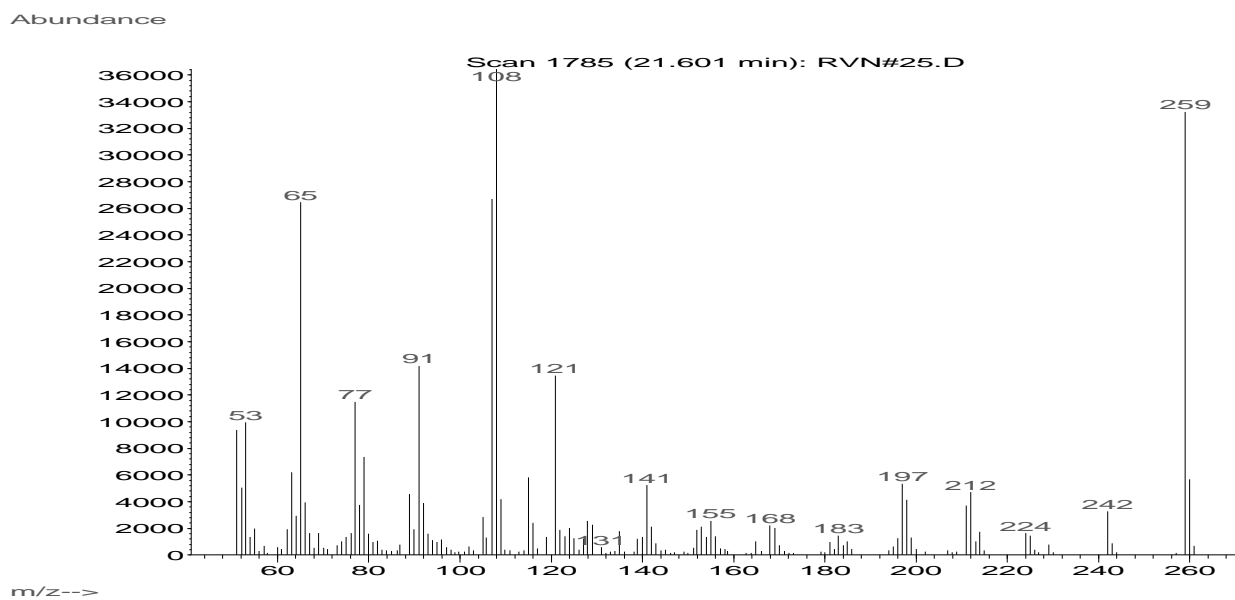


- a) Number of small peaks at $T_r = 3 - 6.2$ min
- b) Number of small peaks at $T_r = 3 - 5.7$ min
- c) Large unidentified peak at $T_r = 6.7$ min

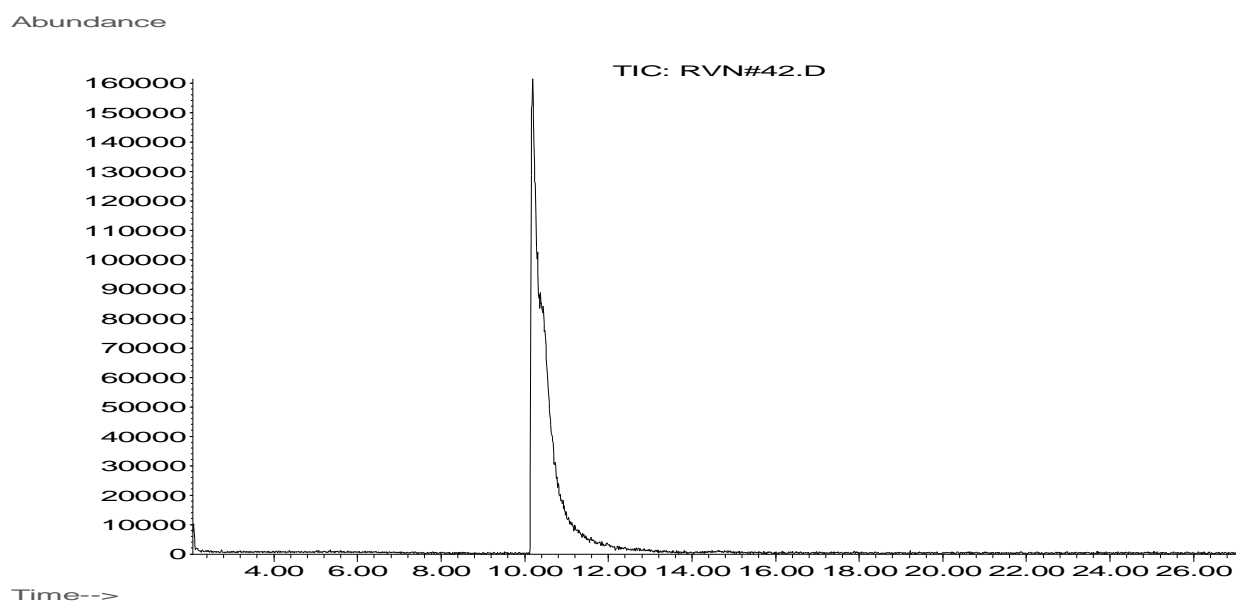
4.2.1 GC-MS TIC (total ion chromatogram) for the side products formed in the scaled-up reaction



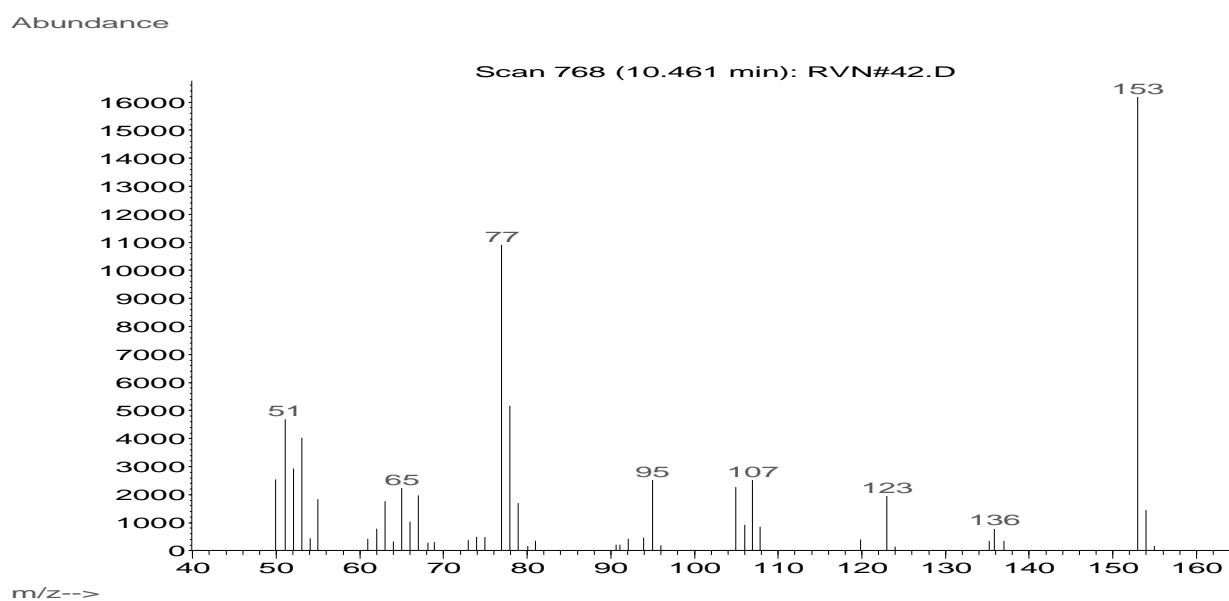
4.2.2 GC-MS spectrum for the major side product formed in the scaled-up reaction



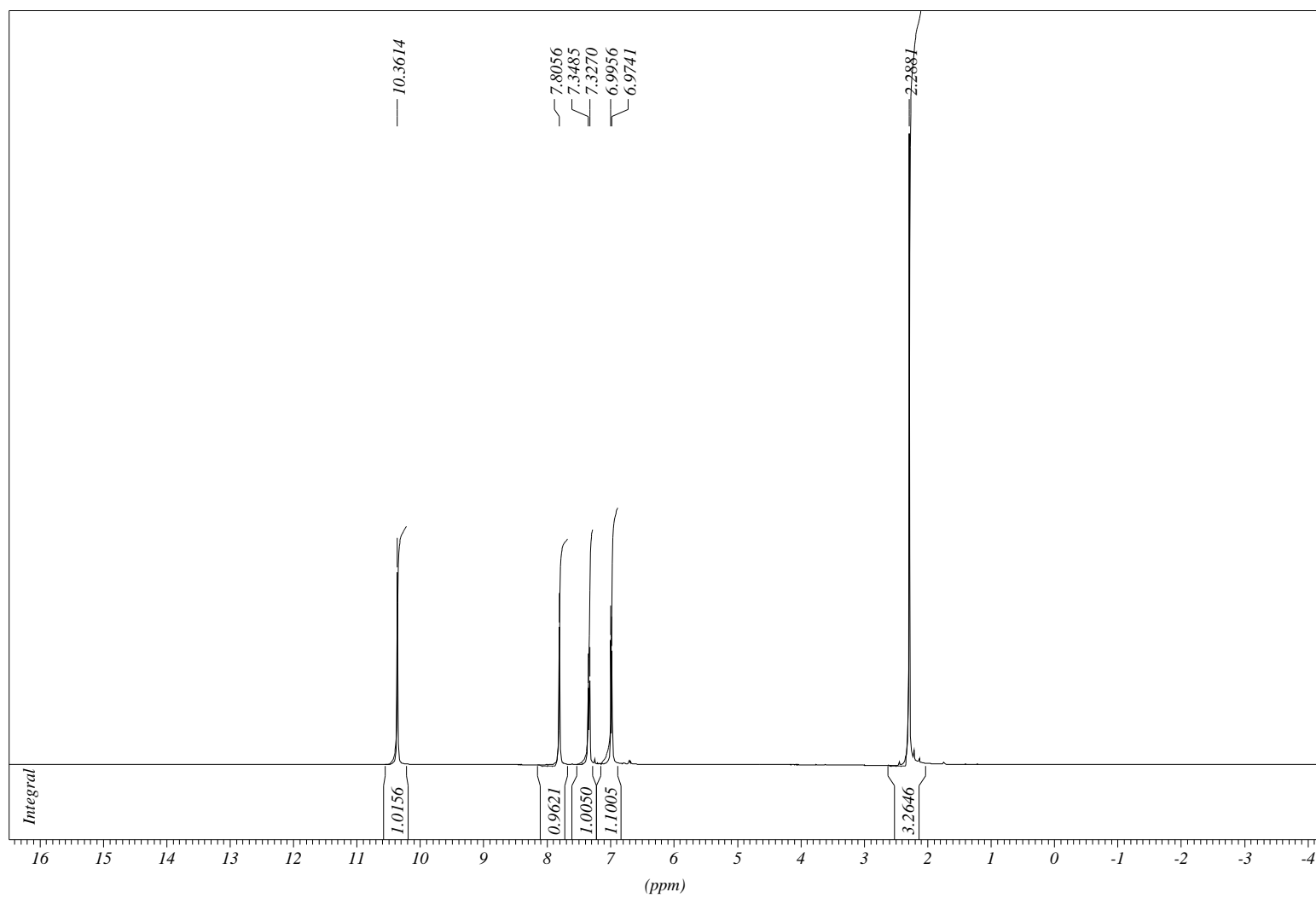
4.3.1 GC-MS TIC (total ion chromatogram) for 4-methyl-2-nitrophenol (2NPC)



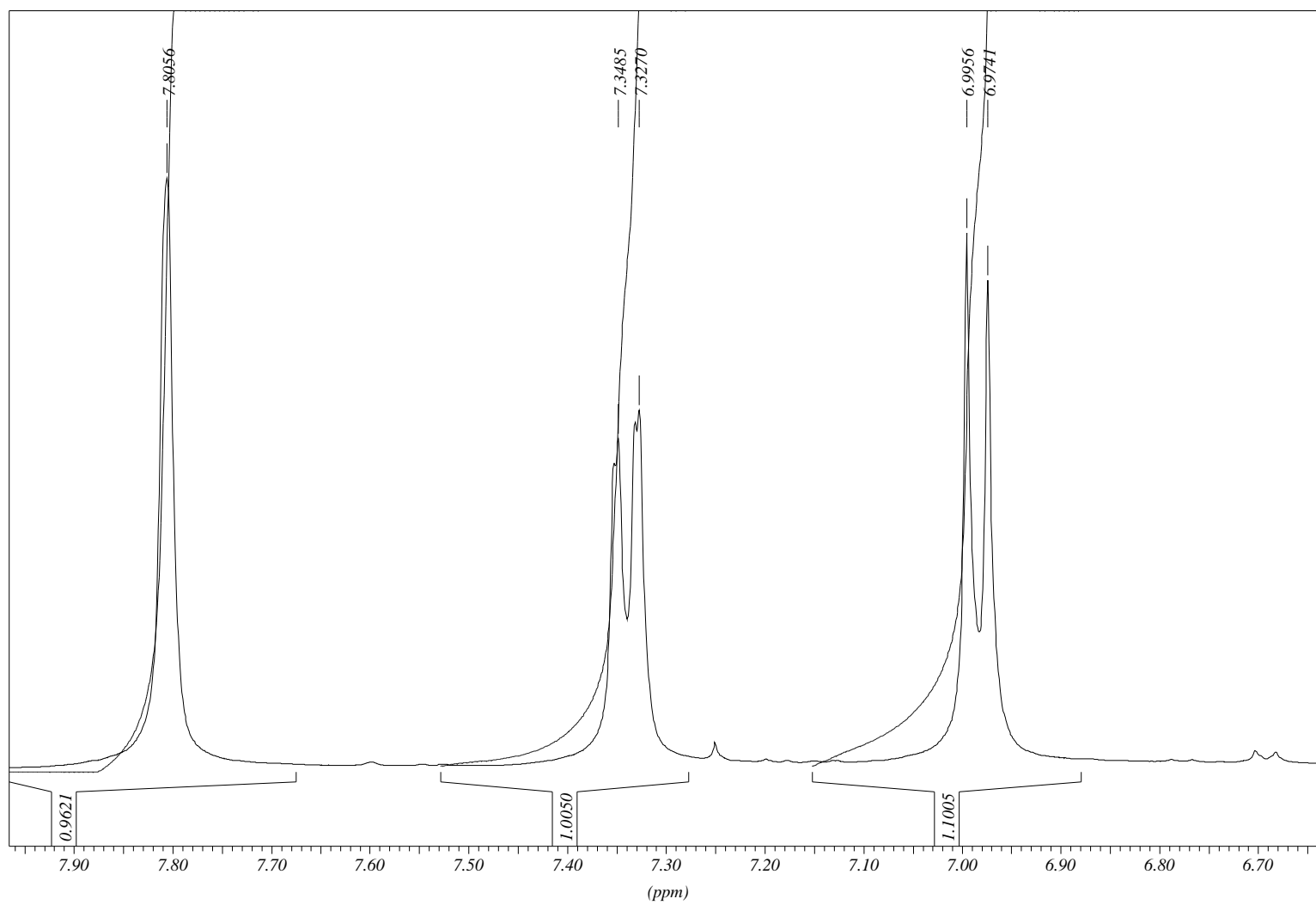
4.3.2 GC-MS spectrum for 4-methyl-2-nitrophenol (2NPC)



4.4.1 H-NMR spectrum for 4-methyl-2-nitrophenol (2NPC)



4.4.2 Expansion of H-NMR spectrum of 2NPC (6.70 and 7.90 ppm)



4.4.3 H-NMR peak assignments for 2NPC

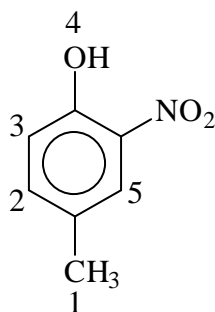


Table (I): Proton assignments for H-NMR

Proton no. ^a	Position (ppm) ^b	Integration	Splitting ^c
1	2.29	3.36	s
2	7.33	1.01	d
3	6.98	1.10	d
4	10.36	1.02	s
5	7.81	0.96	s

^a – protons are numbered on above molecule

^b – position of peak on the NMR spectrum (Appendix 4.4.1)

^c – splitting: s = singlet; d = doublet

(I) LIST OF EQUATIONS

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