SYNTHESIS OF BROMOCHLOROMETHANE USING PHASE TRANSFER CATALYSIS

By

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DECLARATION

I, Lancelot Brooks, hereby declare that the above-mentioned treatise is my own work and that it has not previously been submitted for assessment to another University, or for another qualification.

........................................................................................................................................

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- “And we know that all things work together for good to those who love God, to those who are called according to His purpose” -Romans 8:28.
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SUMMARY

The synthesis of bromochloromethane (BCM) in a batch reactor, using phase transfer catalysis, was investigated. During the synthetic procedure, sodium bromide (100.0g, 0.97mol) along with an excess amount of dichloromethane (265.0g, 3.12 mol) was charged to a reactor containing benzyl triethylammonium chloride (13 mmol), dissolved in 50 ml of water. The bench scale reactions were all carried out in a Parr 4520 bench top pressure reactor coupled to a Parr 4841 temperature controller. The method produced a 50.0 % yield of the product BCM after a reaction time of 12 to 13 hours. The main objective for this investigation was to optimize the abovementioned reaction with respect to yield and reactor throughput.

Quantitative analysis of BCM was performed on a Focus Gas Chromatograph, fitted with a flame ionization detector, and a BP20 column (30m × 0.32mm ID × 0.25 mm). Delta software, version 5.0, was applied for data collection and processing. The injector and detector port were set at 250°C and 280°C, respectively. The oven temperature was set and held at 40°C for a period of 2 minutes, then gradually increased at a rate of 10°C/min to 130°C, with the final hold time set for 1 minute.

An analytical method for the quantitative analysis of BCM was developed, optimized and validated. Validation of the analytical method commenced over a period of three days, and focussed the following validation parameters: Accuracy, precision, and ruggedness. Statistical evaluation of the results obtained for precision showed that the error between individual injections is less than 2% for each component. However, ANOVA analysis showed a significant difference between the mean response factors obtained in the three day period (p-value < 0.05). Thus we could conclude that the response factors had to be determined on each day before quantitatively analyzing samples. The accuracy of the analytical method was assessed by using the percent recovery method. Results obtained showed that a mean percent recovery of 100.18% was obtained for BCM, with the absolute bias = 0.0004, and the percent bias = 0.18%. Hence the 95% confidence intervals for the percent recovery and percent bias are given by:

\((L_Z, U_Z) = (100.56\%, 102.15\%)\),
(L_{PB}, U_{PB}) = (0.56\%, 2.15\%), respectively.

Since the 95\% confidence interval for the percent recovery contains 100, or equivalently, the 95\% confidence interval for percent bias contains 0, the assay method is considered accurate and validated for BCM. In the same manner the accuracy and percent recovery for DCM and DBM was evaluated. The method was found to be accurate and validated for DBM, however, slightly biased in determining the recovered amount of DCM.

With the analytical method validated, the batch production process could be evaluated. A total of six process variables, namely reaction time, water amount, temperature, volume of the two phases, stirring rate, and catalyst concentration, were selected for the study. The effects of the individual variables were determined in the classical manner, by varying only the one of interest while keeping all others constant. The experimental data generated was fit to a quadratic response surface model. The profile plots that were obtained from this model allowed a visual representation of the effect of the six variables.

The experimental results obtained showed that the reaction follows pseudo zero-order kinetics and that the rate of the reaction is directly proportional to the concentration of the catalyst. The reaction obeys the Arrhenius equation, and the relatively high activation energy of 87kJ.mol^{-1} signifies that the rate constant is strongly dependent on the temperature of the reaction.

The results also showed that the formation of BCM is favoured by an increase in the reaction temperature, catalyst concentration, and a high organic: aqueous phase ratio. Thus the synthesis of BCM using phase transfer catalyst could be optimised, to obtain a 100 \% yield BCM, by increasing both the reaction temperature to 105°C, and the concentration of the phase transfer catalyst benzyl triethylammonium chloride to 5.36 mol percent. The reaction time was also reduced to 6 hours.
CHAPTER 1

INTRODUCTION

1.1 Technology of leather production

Leather can be defined as a material that is formed from the hides and skins of animals through the process of tanning. The material is used to manufacture a variety of value added products, which includes furniture, clothing, as well as shoes. In the meat industry, animal skins are considered as a by-product and are made available to tanners by the slaughterhouses. The tanners will convert these skins into more stable materials through the process of tanning and chemical treatment [1].

The leather industry in India is one of the oldest industries but still prominent. The industry contributes to the growth of the country by providing employment to more than 15 million individuals. India is home to about 3000 tanneries that provides the capacity to process up to 700000 tons of skins and hides in a single year. The vast majority of leather and leather products manufactured in India is exported and sold on the international market. Leather exports from the country have grown to an estimate of US $ 2 billion per year [2].

As a result of a more liberal economy, the South African leather industry has experienced a considerable amount of change over the last decade. The relatively un-traded leather and leather products have become highly traded commodities after liberalization. The South African leather industry is currently exporting a significant amount of exotic leather, automotive leather upholstery, as well as bovine hides. In 2001 the export of leather and leather products from South Africa totalled $ 485.94 million, with the automotive leather upholstery constituting 58%, skins and hides 38%, general goods 2%, and footwear 3%, of the total exports. The dawning of trade liberalization in South Africa not only benefited the leather industry in terms of export but also with regard to imported goods. In 2001 imports totalled $328 million, with footwear constituting 59%, skins and hides 27%, and general leather goods 14% of the total imports. According to the ITC reports in 2001, 55% of all leather imports
originated from Australia, followed by Europe with 15%, and South America with 7% [3].

The production of leather from hides and skins involves a sequence of chemical and mechanical processes that is relatively complex in nature. During the production process tanners need to be weary of factors – such as bio-deterioration of the product - that may completely damage or weaken the properties of the leather. Bio-deterioration is a consequence of microbial growth on raw hides during the manufacturing of leather and also storage of the finished product. The humid environment, protein, and lipid content of the raw hides provide the suitable conditions for bacteria, fungi, and actinomycetes to grow. In addition, some tannery agents like protein binders, oils and greases also provides the necessary nutrients for microbial growth to occur [4]. The technical process of leather is illustrated in Figure 1.1.

The impact of the Environmental Health and Safety regulations on the international leather industry has grown significantly in terms of scope as well as complexity. During the past three decades the main emphasis was laid on factors such as the total oxygen demand, and the amount of chromium and sulphide in tannery waste water. However, it is apparent that in years to come environmental controls will be targeting specific chemicals. Substances that are used to limit or control biological activity in the agricultural industry or any other industry may have unfavourable impact on the environment if the substances do not decompose before it is discharged into the environment. A typical example of such substances is biocides that are used to:

a) prevent microbial growth on raw hides and skins being stored or transported,
b) prevent microbial growth on pickled stock being stored and transported,
c) prevent microbial growth during the leather processing stage,
d) prevent microbial growth on simple tanned leather, and
e) prevent microbial growth on finished leather [5].
Figure 1.1: The technical process of leather production [4].
For several decades para-nitrophenol and pentachlorophenol were used to prevent fungal attack during the manufacture of leather, however, due to their toxic properties and poor biodegradability they are no longer used as commercial fungicides. The implementation of legislations opposing the use of pentachlorophenol and para-nitrophenol acted as a driving force for the leather industry to divert to more environmentally friendly fungicides like substituted benzothiazoles. Some of the well known biocides currently used in the leather industry includes, 2-(thiocyanomethylthio)benzothiazole (TCMTB), dimethyldithiocarbamate, N-octylisothiazole, carbendazim, mercaptobenzothiazole, and methylenbisthiocyanate, etc.[6].

1.2 Synthesis of TCMTB

Benzothiazole derivatives, having various applications in industry, are produced in high volumes across the world. 2-Mercaptobenzothiazole for example, is commercially used as a bio-corrosion inhibitor in the galvanic industry and in the cooling system of industrial plants. The agricultural industry makes use of benzothiazole derivatives as herbicides. The majority of industrially manufactured benzothiazoles is employed as vulcanization accelerators during rubber production. Benzothiazole derivatives also act as intermediates during dye production and form part of the structure of various anti-tumour agents. [7, 8]

TCMTB is a broad spectrum, non-chlorophenolic microbiocide that is extensively used to preserve processed leather or wood. It is also employed in the agricultural industry for soil and seed treatment against various diseases of field crops and certain vegetables. TCMTB is poorly soluble in water, thus during formulation commercial emulsifiers are mixed with organic solvents like dimethyl sulphoxide in different proportions. The emulsifiers would contain nonylphenol ethoxylate and calcium alkyl benzene sulphate.

During the treatment of leather, TCMTB is conventionally added to the chrome tanning liquor and the efficiency of the formulation can be ascertained by monitoring the concentration of TCMTB present in the tanning liquor at various time intervals.
However the instability of TCMTB poses a serious problem in the abovementioned analysis as TCMTB tend to degrade:

1. in alkaline solutions,
2. at elevated temperatures,
3. in sulphide containing solutions, or
4. When exposed to light.

The unstable TCMTB would break down to form MBT as the major degradation product [9, 10]. Research studies shows that the broad toxicity of the fungicide however may have damaging effect on the environment. Thus the use of TCMTB as fungicide products is strictly regulated in most countries. [11]. Toxicological data on benzothiazoles revealed that not only is TCMTB acutely toxic but it also induces morphological alterations in fish [8].

TCMTB was initially introduced to the leather industry during the early 1970’s and advances in the study of TCMTB as a fungicide brought forth commercial products that underwent testing in the laboratory as well as in tanneries, in the 1980’s [4,12]. Earlier work performed by Buckman J.D et.al (1970), shows the synthesis of TCMTB by the oxidation of the corresponding thiocyanomethylthio precursor with peracetic acid. A solution of 2-mercaptobenzothiazole and sodium ethoxide in absolute ethanol was kept at < 40°C while chloromethyl thoicyanate was added. The solution was then kept at room temperature for a period of 15 days and filtered to yield crude TCMTB [13].

An environmentally cleaner and simpler method was reported by Muthusubramanian, L. et.al (2005), whereby 2-mercaptobenzothiazole is reacted with a metal salt of a hydroxide. The product of this reaction is then treated with bromochloromethane to form 2-(chloromethylthio)benzothiazole which on further reaction with sodium thiocyanate, and acetone functioning as solvent, yield TCMTB, as illustrated in scheme 1.1.
Scheme 1.1: Synthesis of TCMTB [5].
1.3 Bromine

1.3.1 Overview

Bromine was first discovered in 1862 by Carl Lowig and Antoine-Jerome Balard, at almost the same time. While Antoine-Jerome Balard made his finding known, Carl Lowig had not yet completed his research of the element. Balard isolated bromine from the salts in the water of the Mediterranean and also established its elementary character [14, 15]. The element Br$_2$, is not found in nature but exists as bromine salts in crystal rock [16]. Bromine can be found and recovered from:

1. Seawater as it contains about 100 trillion tons of bromine,
2. mineral deposits that is left after the evaporation of salt lakes,
3. and underground brines

In practice a number of methods can be employed for the recovery of bromine from brines. Among the methods that can be considered are; (1) steam stripping of bromine from the brines, (2) ion exchange, and (3) extraction of bromine subjected to bromine-ion oxidation.

Steam stripping is employed primarily to recover bromine from concentrated solutions of iron bromide. The technology is also used for the recovery of bromine from solutions obtained from carnallite, pharmaceutical as well as organic wastes. In this process chlorine gas is added to the bromide containing material, facilitating the formation of bromine gas. The free bromine gas obtained is then treated with an alkaline or sulfur gas. A draw back of this process is the utilization of chlorine gas which is corrosive and extremely toxic.

Ion-exchange extraction of bromine makes use of highly alkaline anion-exchange resins to selectively absorb elementary bromine in the oxidized form from solutions. Desorption of bromine is achieved through the introduction of sulfite and sodium chloride solution. Even though ion-exchange technology requires the use of expensive ion-exchange resins, and complex equipment, it has the advantage to selectively extract iodine and bromine from solutions where both elements are present.
The solvent extraction method for the recovery of bromine is not employed industrially, as the search for effective bromine extractants still continues. Organic solvents such as kerosene, bromobenzene, hexane, tributyl phosphate, or their mixtures are mainly used, and can be considered for extraction [17].

Studies show that the United States of America was ranked the world’s leading market in terms of bromine production for the year 2006. The bromine consumption for the year 2006 added up to 243000 metric tons, which is valued at $339 million. Figure 1.2 shows the world’s production of bromine in 2006, with the United States dominating the world market [18].

![Pie chart showing world production of bromine in 2006](image_url)

**Figure 1.2: World production of bromine in 2006 [18].**

The prices of bromine compounds increased significantly in 2008. This was a consequence of the remarkable growth in the global market of bromine, and the significant increase of cost, raw materials, transportation, energy, and regulatory compliance [19].
1.3.2 Applications of brominated compounds

Bromine is primarily used in the industry as flame retardants, pesticides, in water treatment, and as drilling fluids during the drilling of boreholes. It is also utilized as intermediates during the synthesis of dyes, insect repellents, perfumes, and brominated pharmaceutical compounds [18, 19]. The use of brominated compounds as flame retardants, pesticides, in photography, and pharmaceutical compounds will be briefly discussed in the succeeding sub-sections.

1.3.2.1 Photography

In the art form of photography, bromine derivatives are renowned for their use in the making of photographic films. Silver bromide which is very sensitive to light, acts as an intensifier in photographic chemicals. The inorganic salt potassium bromide is used to prevent undesired reduction of silver, which may cause fogging in a photograph. The use of bromine in this art form and industry is however diminishing as digital imaging is replacing film usage by the consumer and professional photographers [20, 21].

1.3.2.2 Brominated Flame retardants

The term “flame retardant” refers to any chemical composition that is added to various polymeric compounds, fibre, and paper to prevent or retard ignition of the substance. Flame retardants also reduces the rate at which heat is released from the substance and the amount of toxic gases that may be emitted in the occurrence of a fire. Lastly, the use of flame retardants also increases the on hand time for individuals to flee during a fire [22]. The flame retardant can either be mixed into the polymer during the processing – additive flame retardants - or can react with the polymer thus forming part of the polymeric structure. Based on their modes of action flame retardants are divided into five groups as indicated in table 1.1.
Table 1.1: Grouping of flame retardants based on their mode of action.

<table>
<thead>
<tr>
<th>Mode of action</th>
<th>Description</th>
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<tr>
<td>1) Invert gas dilution</td>
<td>Additive flame retardants are used that generate large volumes of non-flammable gases during thermal decomposition of the polymer. The non-flammable gases will suppress the oxygen concentration lower than the flammability limit.</td>
</tr>
<tr>
<td>2) Thermal Quenching</td>
<td>The flame retardant present in the polymer will decompose endothermally. The temperature of the polymeric surface is thus reduced and the burning of the polymer slowed down.</td>
</tr>
<tr>
<td>3) Physical dilution</td>
<td>The flame retardant increases the heat capacity of the polymeric substance or respectively reduces the concentration of combustible components in the polymer so that it does not exceed the flammability limit.</td>
</tr>
<tr>
<td>4) Protective Coating</td>
<td>In the event of any fire a protective coating is produced on the outer surface of the polymeric substance. This coating insulates the polymer, thus inhibiting the transfer of heat between the flames and the polymer.</td>
</tr>
<tr>
<td>5) Chemical interaction</td>
<td>The flame retardant dissociate to form a multitude of free radicals. These radicals that will disrupt the chain formation and branching steps that is evident during combustion [23].</td>
</tr>
</tbody>
</table>
The most effective flame retardant are those containing phosphorous, antimony, boron, nitrogen, bromine and chlorine as part of their chemical structure, however, determining factors such as cost and efficiency have made brominated flame retardants the most frequently used flame retardant in the current marketplace [24]. It is projected that about 200000 tonnes of brominated flame retardants are manufactured internationally each year with Asia being the principal consumer. In 2001, Asia consumed 56%, followed by America with 29%, and Europe with 15%, of the total market demand [25]. The most widely used brominated flame retardants contain one or more carbon ring. The carbon rings provides stability to the flame retardant, making it efficient in a large number of polymers (26). Brominated flame retardants can be divided into four major classes:

1. Tetrabromobisphenol-A
Tetrabromobisphenol-A is considered the most extensively used brominated flame retardant. Approximately 90% of the total tetrabromobisphenol-A manufactured is utilized as chemically bound flame retardants in epoxy and polycarbonate resins. The remaining 10% is employed as additives in acrylonitrile-butadiene styrene resins and high impact polystyrenes.

2. Hexabromocyclodecane
Hexabromocyclodecane is an additive flame retardant that is used in a wide range of polymers for the purpose of thermal insulation. These polymers are readily made use of in the construction industry. The flame retardant is also functional as back coating of materials in the upholstery industry.

3. Polybrominated diphenyl ethers
Polybrominated diphenyl ethers are a group of additive flame retardants applied in a selection of polymers and foam. During the production process bromine is reacted with diphenyl ether derivative to yield polybrominated diphenyl ether. Commercially, three major types of polybrominated diphenyl ethers are used in consumer products, penta-brominated diphenyl ethers, octa-brominated diphenyl ethers, and deca-brominated diphenyl ethers, respectively.

4. Polybrominated biphenyls
Polybrominated biphenyls were identified as being persistent and bio-accumulative pollutants. The compounds were also classified as potential carcinogens. The EU barred the use of polybrominated biphenyls in electrical and electronic utensils. As a result the use of polybrominated biphenyls is rarely found in recent manufacturing.

Brominated flame retardants have drawn incredible amount of interest over the past ten years. This can be ascribed to their prevalent production and utilization, joined with the extensive data indicating the increase of contamination to the environment, flora and fauna, and human beings. The inadequate information of the possible biological and physiological effects of brominated flame retardants as well as the transformation of specific brominated flame retardants to more toxic products like polybrominated dibenzodioxins and polybrominated dibenzofurans, are also critical issues of concern [27,28]. The European Commission directive on the “Restriction of the use of certain hazardous substances in electrical and electronic equipment” (RoHS) banned the use of certain polybrominated flame retardants in electrical and electronic appliances as from 01 July 2006. The legislation is applicable only if technical substitutes for the polybrominated flame retardant do exist. Countries like Australia, Canada, Korea, and Taiwan, also chose to formally approve and implement the legislation, while similar legislations are planned or have been passed in China, Japan, and in certain states in the United States of America [29,30].

1.3.2.3 Pesticides

Bromine containing pesticides are used to protect food from pests such as bacteria, insects, moulds, rodents, and weeds [30]. Bromine derivatives are also employed as intermediates during the manufacturing of agricultural pesticides and biocides [19]. Methyl bromide, for example, has been used widely as a fumigant to kill termites and as a soil sterilant. The toxicity of this compound is from its ability to transfer an alkyl group to a nucleophilic amino-group or mercapto-group in enzymes, thus altering the enzyme’s normal biological activity [31]. The usage of one of the foremost brominated pesticides – methyl bromide – has radically declined after the 1987 Montreal Protocol prohibited the use of the compound as a pesticide. The classification of the compound as a class I ozone-depleting substance contributed to
the discontinuation of methyl bromide as a pesticide. Wealthy countries had to stop the use of methyl bromide by 01 January 2005. However, nationally methyl bromide had demonstrated to be not easy to replace due to its low cost and efficiency against a great variety of agricultural pests. Methyl bromide was also easy to handle and possessed excellent penetration properties [32].

1.3.2.4 Pharmaceutical

Brominated compounds play an important role during the synthesis of pharmaceuticals. Organic pharmaceuticals can be grouped into two, with the primary group consisting of compounds in which bromine is attached to a carbon atom. The secondary group consists of salts derived from hyrdobromic acid and ammonium organic compounds. Chemical compounds derived from bromine from part of numerous amounts of prescription and over-the-counter drugs. This includes pain relievers, sedatives, and antihistamines. Bromine derivatives also acts as active ingredients in several drugs used to treat pneumonia and cocaine addictions [20, 21, 33].

1.3.3 Natural occurring brominated compounds

The discovery of new and unusual naturally occurring halogenated compounds is truly phenomenal and impossible to contain. More than 3600 halogenated compounds have been identified to date, with brominated natural compounds dominating. The production of brominated natural compounds is evident in many aquatic species like sponges, corals, sea slugs and sea worms. It is also produced by plants, fungi, bacteria, microbes and even in some mammals [27, 34]. Brominated compounds like methoxylated polybrominated diphenyl ethers (MeO-PBDE’s), hydroxylated polybrominated diphenyl ethers (OH-PBDE’s), bromophenols, bromoanisoles, bromoindoles, and polybrominated dibenzo-p-dioxins (PBDD’s) are but a few of the multitude of compounds occurring naturally in marine ecosystems, that have been identified by scientists.
The MeO-PBDE’s have been identified in Baltic Sea organisms like sponges, and dolphins from Australia and the Mediterranean Seas. The natural formation of hydroxylated polybrominated diphenyl ethers and polybrominated dibenzo-\(p\)-dioxins by brown algae and cyanobacteria found in the Baltic Seas has been reported. Studies show that the naturally occurring OH-PBDE’s and MeO-PBDE’s isolated all have their hydroxyl group in the ortho-position. The meta, or para-substituted OH-PBDE’s act as metabolites of PBDE’s. Polybrominated phenols and anisoles have been identified as potential precursors for OH-PBDE’s, MeO-PBDE’s, and PBDD. The precursors are formed in living organisms through the process of enzymatic bromination [35].

The natural occurrence of more than 50 bromophenols has been identified in sea plants and animals. Reports indicate that the bromophenol derivatives isolated from marine organisms are very simple in structure like 2-bromophenol, 2,4-dibromophenol, etc. [26].

1.4 Overview of bromochloromethane

1.4.1 Properties

Bromochloromethane, also known as methylene bromide, is a colourless to yellow liquid having a distinctive odor. The mixed halomethane chemically breaks down upon heating to produce highly poisonous and corrosive fumes which may include hydrogen bromide, and hydrogen chloride gas. These fumes can attack and corrode metal surfaces – for example steel, aluminium, zinc, and magnesium – unless the necessary preventative measures are set in place [36]. The following is a synopsis of the most important chemical and physical properties of bromochloromethane:

- **IUPAC Name**: Bromochloromethane
- **CAS Registry number**: 74-97-5
- **Molecular formula**: \( \text{CH}_2\text{BrCl} \)
Figure 1.3: Molecular structure of bromochloromethane [37].

Table 1.2 below shows the physical and chemical properties of bromochloromethane.

Table 1.2: Physical and chemical properties of bromochloromethane

<table>
<thead>
<tr>
<th>Property</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apparent Colour</td>
<td>Colourless to yellow liquid</td>
</tr>
<tr>
<td>Odour</td>
<td>Sweet, chloroform-like odour</td>
</tr>
<tr>
<td>Boiling point</td>
<td>68°C</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>129.38 g/mol</td>
</tr>
<tr>
<td>Melting point</td>
<td>-88°C</td>
</tr>
<tr>
<td>Relative density (water = 1)</td>
<td>2.0</td>
</tr>
<tr>
<td>Solubility in water</td>
<td>Poor</td>
</tr>
<tr>
<td>Vapour pressure @ 20°C</td>
<td>15.6 kPa</td>
</tr>
<tr>
<td>Relative vapour density (air = 1)</td>
<td>4.5</td>
</tr>
<tr>
<td>Refractive index</td>
<td>1.4808</td>
</tr>
</tbody>
</table>
1.4.2 Toxicology

Bromochloromethane has been studied toxicokinetically only in animals. Based on the results obtained during toxicokinetic studies it is evident that bromochloromethane is metabolized in a similar manner as dichloromethane. The database for the compound in terms of toxicology is relatively small; however the available information indicates that the toxicological profile for bromochloromethane is eminently analogous to that of dichloromethane, with only modest amounts of differences. There is also no information available to substantiate the carcinogenic nature of the compound. An official European Union (EU) regulatory stance on the classification of bromochloromethane has not been implemented; consequently the onus is on the supplier to self-classify. Based on the unavailability of carcinogenic data, bromochloromethane is not classified as a carcinogen by respective suppliers [38].

Bromochloromethane may cause serious eye damage upon contact. It is also irritating to the skin and respiratory system. The lethal dose for 50 percent kill (LD 50) in rats and mouse, during oral consumption, is reported as 5000 mg/kg and 4300 mg/kg, respectively. The lethal concentration for 50 percent kill in mouse after inhalation was reported as 12000 mg/m³. Genetic mutations have also been noticed on tests with bacteria and laboratory animals.

Exposure to bromochloromethane may cause narcotic effect of moderate intensity. Acute effects were reported by firefighters using bromochloromethane as a fire extinguishing agent which includes severe headaches, loss of consciousness, and after exposure, gastric upsets, loss in weight, and slow recovery [39, 40, 41].

1.4.3 Uses of bromochloromethane

Bromochloromethane was invented by the Germans during the mid-40’s to replace carbon tetrachloride that was commonly used in fire extinguishers. Carbon tetrachloride would generate highly poisonous by-products when released onto a fire, which caused a great concern in air crafts and tanks. Bromochloromethane was slightly less poisonous and more efficient than carbon tetrachloride, and was used in
fire extinguishers up until the late 1960’s. The National Fire Protection Association (NFPA) officially banned the use of bromochloromethane in fire extinguishers in 1969, and replaced it with less toxic and more efficient agents such as halon 1211 and halon 1301. In consequence of the ozone depleting potential, the manufacturing of fire extinguishers making use of bromochloromethane was banned in January 2002. [37]

Commercially it is utilized as an explosion suppression agent, alternatively as an intermediate in the production of several insecticides. Along with dibromomethane, bromochloromethane may also be used as a solvent during bromination reactions, in particular for the synthesis of polybrominated aromatics and polymers. In the leather industry, bromochloromethane is used during the synthesis of the microbiocide - methylene bisthiocyanate (MBT), as illustrated in equation 1.7 [42].

**Equation 1.1: Synthesis of methylene bisthiocyanate (MBT)**

\[
1 \text{CH}_2\text{X}_2 + 2 \text{MSCN} \rightarrow \text{CH}_2(\text{SCN})_2 + 2\text{MX}
\]

Where: \(X = \text{Br, Cl}\)

\(X_2 = \text{ClBr}\)

\(M = \text{Na, K}\)

Bromochloromethane is also during the synthesis of TCMTB as already mentioned and illustrated in Scheme 1.1. Commercially biocidal formulations consisting of equal amount of MBT and TCMTB are available. This formulation combines the antimicrobial and fungicidal properties of MBT and TCMTB, respectively, and is appropriately used over an extensive array of applications in tanneries.
1.5 Synthesis of bromochloromethane

As in the case with most chemical compounds, there are a number of possible routes, either from different starting materials, or from the same starting materials, that can be utilized for the production of bromochloromethane. It is important that all the potential routes be evaluated so as to ensure the most economically viable and technically sound method is selected to meet all legislatory requirements as well as the quality specifications for the product.

1.5.1 Synthesis of bromochloromethane using dimethylformamide

Sumitomo Chemical Co. reported in 1965, the synthesis of bromochloromethane by heating a mixture of dimethylformamide and ammoniumbromide at 95°C, and stirring until a homogenous solution is obtained. Dichloromethane was then introduced into the solution at a rate of 10 g/ min. while the temperature is kept at 95 to 100°C. The gas formed was condensed and distilled and rectified in a closed system for 10 hours. The yield of bromochloromethane was 95 % with respect to dichloromethane [43].

During this synthetic process a highly aprotic solvent- dimethylformamide- is used. This solvent is expensive, toxic and very difficult to remove during purification.

1.5.2 Synthesis of bromochloromethane using ethylene glycol monoethylene ether

Bromochloromethane can also be prepared by heating dichloromethane with sodium bromide in water and ethylene glycol monoethyl ether or diethylene glycol monoethyl ether at 140°C for 1.5 hr in a sealed tube. Kobertz P., et.al., reports a mixture of dihalomethanes being obtained as product. The product comprised of dibromomethane 32 mol%, bromochloromethane 45 mol%, and dichloromethane 37 mol % [44].

This method also makes use of expensive solvents- ethylene glycol monoethyl ether or diethylene glycol monoethyl ether- which needs to be recovered and re-used. A
mixture of dihalomethane is obtained as product, which need to be purified using fractional distillation.

1.5.3 Synthesis of bromochloromethane using hydrogen bromide gas

Hydrogen bromide gas can be reacted with dichloromethane in the liquid phase or vapour phase, in the presence of anhydrous aluminium chloride or activated carbon, at elevated temperatures to yield bromochloromethane. Hermann, passed 2 mol hydrogen bromide gas into dichloromethane in the presence of anhydrous aluminium chloride at 30 to 35°C for 2 hours. The reaction yielded bromochloromethane containing 1 % dibromomethane. The halogen acids that evolved contained 77 mol percent hydrochloric acid and 23 mol percent hydrogen bromide.

In the vapour phase, 1 mol hydrogen bromide and 5 mol dichloromethane was passed over active carbon or anhydrous aluminium chloride at 250°C to yield bromochloromethane and a small amount of dibromomethane [45].

Equation 1.2: Synthesis of bromochloromethane using hydrogen bromide gas

\[
\text{CH}_2\text{Cl}_2 + \text{HBr} \rightarrow \text{AlCl}_3 \rightarrow \text{CH}_2\text{BrCl} + \text{HCl}
\]

This method involves the use of corrosive and toxic chemicals – hydrogen bromide and aluminium chloride- and gives yield to the by-product dibromomethane.

1.5.4 Synthesis of bromochloromethane using hydrogen bromide and chlorine gas

By passing a gaseous stream of methylene chloride, bromide or hydrogen bromide and chlorine through a heated stainless steel tube at 250°C to 340°C a mixture of all
possible bromochloromethanes were obtained, which were separated by careful fractional distillation. The mixture consisted of CH₂ClBr, CHClBr₂, and CClBr₃ [46].

The method involves the use of highly corrosive gases at high temperatures and gives yield to a complex mixture of by-products from which bromochloromethane has to be separated by careful fractionation with consequent higher costs.

1.5.5 Synthesis of bromochloromethane using phase transfer catalysis

Muthusubramanian L. et al, developed a simple, environmentally friendly cleaner method of preparing bromochloromethane by reacting ammonium or metal halide with an halogenating agent in the presence of small amount of phase transfer catalyst, which is non hazardous and non-toxic.

Sodium bromide along with excess dichloromethane was charged to a reactor containing a small quantity of benzyltriethyl ammonium chloride with water. The reaction blend was stirred at 90°C for the duration of 12 to 13 hours. Subsequently, the reactor was allowed to cool to room temperature and the organic phase separated from the solid sodium chloride. The organic phase was then subjected to fractional distillation to yield 50% bromochloromethane [47].

1.6 Halogen exchange reaction – Finkelstein reaction

The carbon-halogen bonds of the alkyl halide, or any alkyl halide, results from the overlap of a carbon sp³ hybrid orbital with a halogen orbital. Thus, alkyl halide carbon atoms have an approximately tetrahedral geometry. Halogens increase in size going down the periodic table so the bond lengths of the halomethanes increase accordingly. However, the C-X bond strengths decrease going down the periodic table. Halogens are more electronegative than carbon thus the C-X bond is polar with the C being a slight positive charge (δ+) and the halogen a slight negative (δ-). This polarity results in a substantial dipole moment for all the halomethanes, and implies that the alkyl halide C-X carbon atom should behave as an electrophile in polar reactions. Thus when alkyl halides are reacted with a nucleophile they do one
of two things; the X group can be substituted by the nucleophile, or elimination of HX can occur that will give way to an alkene [48].

Alkyl bromides are often more reactive and therefore synthetically more useful than the corresponding chlorides. Alkyl chlorides are generally cheaper and easily available. However, the conversion of the alkyl chlorides into alkyl bromides has received increasing attention recently. Halogen exchange is generally accomplished with a metal salt in a homogenous solution when a polar solvent is used– Finkelstein reaction.

The Finkelstein reaction, named after the chemist Hans Finkelstein, is an $S_N 2$ reaction that entails the substitution of one halogen atom for another as illustrated in equation 1.9.

**Equation 1.3: The Finkelstein reaction**

$$ R-Cl + M^+ Br \rightleftharpoons R-Br + M^+ Cl^- $$

The halogen exchange reaction is in a state of equilibrium but can be pushed to completion by taking advantage of the degree of variation in the solubility of halide salts. Alternatively, an excess amount of the halide salt can be used [49].

**1.7 Phase transfer catalysis**

**1.7.1 Overview**

The introduction of phase transfer catalysis provided an effective, alternative method to achieve halogen exchange in bi-phase systems. The technology of phase transfer catalysis has been successfully employed for more than thirty years in the manufacturing organic compounds. The mechanistic features of phase transfer catalysis have been extensively studied to attain concrete insight of the technology. During mid seventies phase transfer catalysis became the method for conquering difficulties of mutual solubility. It also offered the potential for the activation of anions. This method was originally employed to facilitate the reaction of ionic compounds
and organic, hydrophilic substances in the presence of low polarity solvents. Later works shows phase transfer catalysis being used in bi-phase systems for the transfer of molecules (cation or neutral) from one phase to another [50].

1.7.2 Mechanism
The mechanistic explanation towards the functioning of phase transfer catalysis was initially put forward in 1971. Studies performed by Starks indicated that a quaternary ammonium halide (Q⁺X⁻) – commonly used as phase transfer catalysts - that was dissolved in an aqueous medium will undergo anion exchange at or in close proximity to the border of the two phases. Within the aqueous phase, anion exchange can now occur between the phase transfer catalyst and the specific anion present. The lipophilic nature of the newly formed ion-pair (Q⁺Y⁻), facilitates the migration of the ion-pair (situated in the aqueous phase), to the non-aqueous/organic phase. This phenomenon is also referred to as the “phase transfer” step. Within the organic phase, solvation of the anion is not as strong as observed in the aqueous phase, thus nucleophilic displacement between the ion-pair and substrate is highly favored. The reaction of nucleophilic displacement will yield our product and a new ion-pair which can migrate back to the aqueous phase, continuing with the cyclic movement in the two-phase system. For any particular substance to operate as a phase transfer catalyst it is imperative that the ion-pair formed have some degree of solubility in the organic phase. Secondly, during the phase-transfer step, the ion-pair should be in a highly active state [51]. The mechanistic explanation of phase-transfer catalysis is clearly depicted in scheme 1.2.

\[
\begin{align*}
\text{Organic Phase} & \quad QY + RX \rightarrow RY + QX \\
\text{Interface} & \quad \uparrow \quad \downarrow \\
\text{Aqueous Phase} & \quad Q^+Y^- + X^- \rightarrow Y^- + Q^+X^- 
\end{align*}
\]

Scheme 1.2: Mechanism of phase transfer catalysis reaction
1.7.3 Catalyst

Phase transfer catalysts readily available on the commercial market include quaternary ammonium and phosphonium salts, open-chained polyethers, and crown ethers, as illustrated in Figure 1.4. More complex structures like the octopus molecules and silacrowns may also be used as phase transfer catalysts; however most research has been done using the simpler and readily available catalysts. Phase transfer catalysts are utilized to catalyze a great selection of organic reactions, which includes anion exchange, aromatic halogen exchange, the Friedel-Crafts reaction, and the Wittig reaction, etc.[52].

![Fig 1.4: Representative phase transfer catalysts](image-url)
The choice of catalyst is an important factor in phase transfer catalysis. In terms of anion transfer reactions the following characteristics needs to be taken in consideration:

- The catalyst should be cationic and in possession of ample organic structure so that it, along with the desired anion can migrate from the aqueous phase to the organic phase.
- The effective bonding between the cation and anion must be adequately “loose” to allow anion reactivity
- The catalyst need to be stable under the respective reaction conditions
- Availability or simplicity of catalyst preparation
- Cost
- Ease of removal or recovery of catalyst
- Selectivity in catalyst activity
- Whether anhydrous conditions are desirable or not [53]

1.7.4 Industrial uses of phase transfer catalysis

The technology of phase transfer catalysis not only advances reactions between immiscible phases but in batch processes it presents some important advantages, which includes:

- Increase of reaction rates
- Increase of selectivity and product specificity
- Lowering the energy requirements for the reaction to occur
- The utilization of non-toxic, reasonably priced, recoverable solvents
- The utilization of reactants in liquid form that may also function as solvent
- The utilization of commercially available and reasonably priced catalysts
- The utilization of low-cost salts for anion generation, and
- The utilization of low-cost oxidants.
The abovementioned factors all add to the efficiency of batch processes with regard to the size of the equipment needed to execute the reaction, the purity of the obtained product, as well as the ease of catalyst recovery [54].

The most prominent limitation for using phase transfer catalysis in batch processes is in relation to the catalyst. Quaternary ammonium and phosphonium salts tend to break down at approximately 120°C to 150°C. The temperature, at which the salts decompose, decreases when bases or specific nucleophiles form part of the reaction. Decomposition precedes either by means of nucleophilic attack or Hoffmann degradation reaction.

Equation 1.4: The Hoffmann degradation reaction

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{NH}_2 \\
\text{CH}_3 & \quad 1) \text{CH}_3\text{I} \\
& \quad 2) \text{Ag}_2\text{O}, \text{H}_2\text{O},\Delta
\end{align*}
\]

The separation of the catalyst from the product as well as recycling of the catalyst after use may also pose problems. Other trait features of different catalysts which may represent possible disadvantages include their asking price, toxicity, and shortage of local waste treatment capability [55].
SUMMARY

After considering all possible routes for the synthesis of bromochloromethane, a selection needed to be made regarding the most suitable method that can be utilized. Certain aspects, such as cost of catalyst, availability or raw materials, toxicity of raw materials, and complexity of synthesis, needed to be taken into account. The method also needs to meet all legislator requirements as well as equipment and condition restrictions of the industrial partner.

Of the potential methods discussed, the synthesis of bromochloromethane using phase transfer catalysis appears to offer substantial advantages over the other methods. The method does not require the use of expensive solvents or toxic chemicals as in the other methods mentioned. The method makes use of metal halides such as sodium bromide and dichloromethane. Quaternary ammonium compound - benzyl triethylammonium chloride - is used as phase transfer catalyst. This catalyst is extensively used in literature, easily available and relatively low in cost. The reaction can also be performed in moderate temperatures in a batch reactor, which imply that equipment cost will be relatively low. The synthesis also produces only one significant by-product which will simplify product purification.

In view of the above considerations, we have chosen to investigate phase transfer catalysis for the synthesis of bromochloromethane. This thesis is divided into two parts: The first section focuses on the validation of the analytical method, and the second part explores the factors that may influence the reaction yield in a batch reactor system.
RESEARCH HYPOTHESIS

The synthesis of bromochloromethane using phase transfer catalysis in a batch reactor can be optimized with respect to yield and reactor throughput.

AIMS AND OBJECTIVES

The overall objective of the study is to optimize the phase transfer catalysed reaction of dichloromethane with sodium bromide in a batch reactor, with respect to yield and reactor throughput.

To achieve the abovementioned objective the study was divided in phases whereby the following goals had to be achieved:

- Develop and optimize an analytical method for the quantitation of bromochloromethane by means of gas chromatography.
- Synthesize and purify bromochloromethane, to be used as a standard during the validation procedure.
- Characterize the isolated bromochloromethane standard using Infra-red spectroscopy and GC-MS.
- Validate the analytical method.
- Identify the reaction variables that could have a significant influence on the conversion of dichloromethane to bromochloromethane.
- Experimentally study the identified reaction variables.
- Statistically evaluate experimental results.
- Analyse and interpret experimental results.
- Test the identified conditions for optimization experimentally.
2.1 Materials

All reagents used during the synthesis of bromochloromethane as well as those used as GC standards, together with their sources and respective grades, are listed in Table 2.1. Unless otherwise stated, all regents were used as received.

Table 2.1: Reagents used for synthesis and analysis

<table>
<thead>
<tr>
<th>Chemical Name</th>
<th>Formula</th>
<th>Source</th>
<th>Grade A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dichloromethane</td>
<td>CH₂Cl₂</td>
<td>Minema</td>
<td>AR</td>
</tr>
<tr>
<td>Sodium bromide</td>
<td>NaBr</td>
<td>ACE Pty. Ltd.</td>
<td>AR</td>
</tr>
<tr>
<td>Dibromomethane</td>
<td>CH₂Br₂</td>
<td>BDH Chemicals</td>
<td>AR</td>
</tr>
<tr>
<td>Chloroform</td>
<td>CHCl₃</td>
<td>SMM Instruments</td>
<td>AR</td>
</tr>
<tr>
<td>1-Pentanol</td>
<td>CH₃(CH₂)₄OH</td>
<td>Fluka</td>
<td>AR</td>
</tr>
<tr>
<td>Benzyltriethylammonium chloride</td>
<td>C₆H₅CH₂N(C₂H₅)₃Cl</td>
<td>Aldrich</td>
<td>AR</td>
</tr>
</tbody>
</table>

A: AR = Analytical Reagent

2.2 SYNTHETIC PROCEDURES

2.2.1 Synthesis of bromochloromethane

Sodium bromide (100.0 g, 0.97mol) along with excess dichloromethane (265.0 g, 3.12mol) was charged to a reactor containing a small quantity of benzyl triethylammonium chloride (13 mmol) along with 50 ml water. The reaction was
stirred (800 rpm) at 90°C for 12-13 hr. The presence of a phase transfer catalyst in the reaction, allows halogen exchange in the bi-phase system to be achieved. Thus bromochloromethane is formed in the organic phase and sodium chloride in the aqueous phase. However sodium bromide is more soluble in water than sodium chloride and the high concentrations of bromide salts forces the chloride salt to precipitate out of solution. The reaction blend was then allowed to cool to room temperature, and the organic phase separated from the solid sodium chloride. The organic phase was then subjected to fractional distillation to separate dichloromethane from bromochloromethane. The fraction collected in the boiling range 60°C to 65°C was analyzed by GC-MS and IR spectroscopy to confirm the structure of the resulting halomethane. The following fragmentation pattern was obtained from the GC-MS: (M₂ = 129 (M⁺), 93 (M₂ - 36), 49 (M₂ – 80)

![GC-MS chromatogram for bromochloromethane](image)

**Figure 2.1:** GC-MS chromatogram for bromochloromethane
The IR spectrum of the compound shows the characteristic absorption bands at 605.26 cm\(^{-1}\) for C-Br bond, 733.01 cm\(^{-1}\) for C-Cl bond and, 2986.81 cm\(^{-1}\) for an aliphatic C-H stretching of the methylene group, as illustrated in Figure 2.1. The purity of the isolated bromochloromethane, determined using gas chromatography, was found to be 94 %.

**Figure 2.2:** Infra-red spectrum of isolated bromochloromethane
2.2.2 Batch reactor

Bench scale reactions for the synthesis of bromochloromethane were all carried out in a Parr 4520 bench top pressure reactor coupled to a Parr 4841 temperature controller. A glass liner was inserted to limit pitting corrosion of the stainless steel reactor vessel.

Figure 2.3: Parr 4520 bench top pressure reactor.

Bomb material : T316 Stainless steel
Maximum pressure : 130 Bar
Maximum temperature : 350°C
Volume : 2000 cm³

The reactor was pressure tested by adding 1000 cm³ of water in the reactor vessel and purging the system with nitrogen gas. The system was closed, temperature gradually increased from 20 °C to 90°C while stirring, and the change in pressure
monitored. The pressure remained constant at 6 Bars as the temperature increased to 90°C.

2.2.3 Product purification

Separation of the product-bromochloromethane-from the starting material-dichloromethane-were achieved through fractional distillation. The fractionating column employed had a length of 600mm and was packed with spherical glass rods. The packing material had an average length of 25mm and width of 5mm. The typical fractional distillation set-up is illustrated in Figure 2.4.

Figure 2.4: Fractional distillation setup [56].
The analytical technique, fractional distillation, follows the basic principle as simple distillation with the exception of a fractionating column that is located between the condenser and the reaction flask. The fractionating column is usually packed with glass rods or glass beads which effectively improves the separation between components. The packing material can be considered as “theoretical plates” which provides continuous distillation of the test mixture as a sequence of condensation and evaporation steps occurs within the column. Highly volatile fractions will migrate fast towards the top of the column and condense out first from the column whereas the less volatile tend to stay at the base of the column, thus optimum separation and purity can be achieved.

The organic phase that was separated from the solid sodium chloride was transferred to a 250 cm$^3$ round bottomed flask and attached to the fractional distillation apparatus. The mixture was stirred and gradually heated and fractions collected at different temperature ranges as the distillation process proceeded. The fractions collected were weighed and analysed using gas chromatography. The first fraction collected between 36 °C and 40 °C, consisted predominantly of the starting material- dichloromethane. A second fraction was then collected between 40 °C and 45 °C. This fraction constituted mainly of the dichloromethane however small amounts of the bromochloromethane could also be observed. The third fraction collected between 45 °C and 50 °C also contained a mixture of dichloromethane and bromochloromethane. The final fraction collected eluted between 60 °C and 65 °C and showed bromochloromethane as the predominant peak with a minute amount of dichloromethane. The latter fraction was re-distilled to purify the isolated bromochloromethane.
2.3 ANALYTICAL TECHNIQUES

2.3.1 Gas Chromatography

Gas chromatographic analysis was executed on a Focus Gas Chromatograph, equipped with a Flame Ionization Detector was used. The data was acquired from the detector by means of a mercer personal computer equipped with the Delta software, version 5.0 for the recording and integration of chromatograms. The following instrumental conditions were used: Column: BP20 (Polyethylene Glycol): 30m × 0.32mm ID × 0.25mm. The injector port and detector temperatures were set at 250 °C and 280 °C, respectively, and the column oven temperature programmed as shown in table 2.2.

Table 2.2 GC conditions

<table>
<thead>
<tr>
<th>Initial column temperature</th>
<th>40°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial hold time</td>
<td>2 min</td>
</tr>
<tr>
<td>Heating rate</td>
<td>10 °C/min</td>
</tr>
<tr>
<td>Final column temperature</td>
<td>130 °C</td>
</tr>
<tr>
<td>Final hold time</td>
<td>1 min</td>
</tr>
</tbody>
</table>

2.3.2 Gas chromatography- Mass Spectrometry

Gas chromatography-mass spectrometry analysis was performed on a Thermo Finnigan GC-MS fitted with a mass selective detector, a RTX 35 ms column (length 30 m × 0.25 mm ID × 0.25 μm thickness). The GC-MS was connected to a Hewlett Packard personal computer equipped with Excalibur software, version 1.3. Table 2.3 summarizes the GC-MS conditions used for analysis.
Table 2.3: GC-MS conditions

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial column temp.</td>
<td>40 °C</td>
</tr>
<tr>
<td>Initial hold time</td>
<td>5 min</td>
</tr>
<tr>
<td>Heating rate 1</td>
<td>2 °C/min</td>
</tr>
<tr>
<td>Temperature 1</td>
<td>70 °C</td>
</tr>
<tr>
<td>Column hold time</td>
<td>2 min</td>
</tr>
<tr>
<td>Heating rate 2</td>
<td>10 °C/min</td>
</tr>
<tr>
<td>Final temp.</td>
<td>180 °C</td>
</tr>
<tr>
<td>Final hold time</td>
<td>2 min</td>
</tr>
<tr>
<td>Injector temp.</td>
<td>250 °C</td>
</tr>
<tr>
<td>Split ratio</td>
<td>1:30</td>
</tr>
<tr>
<td>Carrier gas</td>
<td>Helium at constant flow (1.0 ml/min)</td>
</tr>
<tr>
<td>Run time</td>
<td>35 min</td>
</tr>
<tr>
<td>MS-mass range</td>
<td>30-1000 amu</td>
</tr>
</tbody>
</table>

2.3.3 Infra-red spectroscopy

Infra-red analysis was performed on Bruker-Tensor 27 spectrometer. Data was acquired by means of a personal computer equipped with OPUS software, version 4.

Samples for analysis were prepared by pressing 1 to 2 drops between two potassium bromide cells to achieve a thin liquid film. The infra-red spectrum for each sample was obtained in the range of 4000 – 400 cm⁻¹.
2.4 VALIDATION PROCEDURE

2.4.1 Summary

Validation of the analytical procedure was carried out to test the ruggedness, accuracy and precision of the GC assay method. The validation procedure was executed over a period of three days. On each day 1 µl of a prepared standard solution was injected five times and the response factors for each component were calculated using the peak areas of the components. Known sample solutions were then accurately prepared and analysed. The masses of the components in the sample solutions were calculated using the response factors obtained from the standard solution. The error was thus evaluated by using the calculated masses of the components as a percentage of the actual mass.

2.4.2 Preparation of standard solution

A standard solution was prepared by weighing 1,875g of dichloromethane, 0,375g bromochloromethane, and 0,25g dibromomethane into 50ml volumetric flask along with 0,375g chloroform as internal standard. The solution was shaken and filled to volume with solvent (1-Pentanol). The elution of components during gas chromatography analysis is illustrated in Figure 2.5.

![GC Chromatogram for standard solution.](image)

Figure 2.5: GC Chromatogram for standard solution.
2.4.3 Preparation of sample solutions

A series of sample solutions were prepared in 50 ml volumetric flasks as illustrated in table 2.4.

Table 2.4: Shows the theoretical mass (g) for each component.

<table>
<thead>
<tr>
<th>Component</th>
<th>Sample A</th>
<th>Sample B</th>
<th>Sample C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dichloromethane</td>
<td>2.250</td>
<td>2.00</td>
<td>1.750</td>
</tr>
<tr>
<td>Bromochloromethane</td>
<td>0.250</td>
<td>0.375</td>
<td>0.500</td>
</tr>
<tr>
<td>Dibromomethane</td>
<td>0.0</td>
<td>0.125</td>
<td>0.250</td>
</tr>
<tr>
<td>Chloroform</td>
<td>0.375</td>
<td>0.375</td>
<td>0.375</td>
</tr>
</tbody>
</table>

2.4.4 Calculation of response factors

The following equation 2.1 was used to calculate the response factors of components in the standard solution.

Equation 2.1: Calculation of response factors

\[ F = \frac{A_x M_x}{M_x A_s} \]

Where: 
- \( F \) = Response factor
- \( A_x \) = Area of component x,
- \( M_x \) = Mass of component x,
- \( A_s \) = Area of the internal standard, and
- \( M_s \) = Mass of internal standard.
2.4.5 Calculating mass of component x

Through simple manipulation of equation 2.1 the masses of the component x in the sample solutions were calculated. Equation 2.2 illustrates this calculation.

Equation 2.2: Calculating mass of component x

\[ M_x = \frac{A_x M}{F \cdot A_s} \]

2.5 CALCULATIONS

In studying the effect of different reaction variables, the yield needed to be calculated. For a typical chromatogram only the major peaks i.e. dichloromethane, bromochloromethane, and dibromomethane were accounted for. Solvent peaks as well as minor unknown peaks were ignored. The total minor unknown peaks contributed an estimate of approximately 1, 0 % of the total peak area.

2.5.1 Yield

The molar yield of the product- bromochloromethane- was calculated by dividing the actual percent mol of product obtained with the theoretical mol percent. The theoretical mol percent were calculated with respect to the limiting reagent – Sodium bromide.

\[ Y = \frac{Actual\ Yield}{Theoretical\ Yield} \]
CHAPTER 3

RESULTS AND DISCUSSION

3.1. Validation of analytical method

3.1.1. Methodology

The precision and accuracy of any qualitative analysis depends on a number of factors that needs to be taken into account before starting any analysis. Firstly, special care needs to be taken during the preparation of samples. Samples should be prepared accurately, as per set specifications. Secondly, the precision and accuracy of all instruments used during quantitative analysis, needs to be verified prior to use. The robustness of the functional analytical method should also be taken into account, and lastly, the integration of peak areas should be executed accurately and consistently for all samples during analysis. Thus the proficiency and sound technique of the analyst is imperative to ensure that samples are accurately prepared and processed. Correspondingly, it is also important that instrument conditions are kept as per set specification and reproducible from test to test [57].

Most frequently chemist makes use of the internal standard method of analysis to enhance the accuracy and robustness of the analytical method. The internal method method of analysis is based on the assumption that it is possible to compensate for differences in instrument conditions like the flow rate, column condition, column temperature, injection volume, as well as errors introduced during sample preparation [57].

The method is executed as follows. A standard compound (the internal standard) is added to the original sample at an accurately known concentration determined by weighing. The standard compound is selected according to the following decisive factors:

1. The peak of the standard should not overlap with the peaks of other compounds
2. The retention of the standard should not be too different from those of the components to be quantified

3. The volatility of the standard should not be too different from that of the significant sample components

4. The concentration of the standard within the sample should be of the same amount as those of the analyte components. [58]

Based on the abovementioned criteria trichloromethane was selected as internal standard during quantitative analysis of bromochloromethane, using gas chromatography.

Validation is an important feature in any method of measurement because of its close relation to the quality of results. According to the United States Food and Drug Administration (FDA) guidelines, validation is defined as the procedure by which proof is obtained and documented, substantiating the ability of a specific process to consistently manufacture a product that will meet its requirements in terms of quality and predetermined specifications [59]. The European Union (EU) guidelines however define validation as the act to attest, in agreement with good manufacturing practices, that any activity, procedure, equipment, system, etc., will actually lead the anticipated results. More specifically, the validation of an analytical method refers to the procedure by which evidence is obtained through experimental tests to confirm that the performance characteristics of the specific method complies to the requirements for the intended analytical function [49]. The performance characteristics of the analytical method of testing procedure can be assessed through a set of analytical validation parameters. These parameters include accuracy, precision, limits of detection and quantitation, selectivity, range, linearity, and ruggedness. Among these parameters- accuracy, precision, linearity, and ruggedness are the primary parameters. In the following section, the primary parameters are defined [59].

1. Accuracy

The accuracy of an assay method can be defined as the closeness of the assay result acquired by the assay method to the true value. Accuracy means there is no
systematic error in the assay method. Even though the validation parameter can be measured in a number of ways, the method employed should be suitable to the sample matrix. Any of the following methods can be employed to establish the accuracy of an analytical method.

a) A sample of which the concentration is known can be analyzed using the specified analytical method and the obtained value can be compared with the true value.

b) Spiked-placebo recovery method: A pure active ingredient of which the quantity is known, is added to a test mixture that contains all other components with the exception of the active. The resulting mixture is analyzed and the end results compared with the projected results.

c) Standard addition method: A test sample is analysed and the results documented. The sample is then analysed for the second time subsequent to the addition of a pure active ingredient of which the quantity is known. The variation between the assays is compared with the projected results [60].

2. Precision

Precision refers to the degree of closeness between multiple data points measured under identical analytical parameters. The International Conference of Harmonization (ICH) stipulated that precision can be sub-divided into three major components, compromising of reproducibility, repeatability, and intermediate precision, respectively. The precision of analytical methods is generally expressed in terms of the standard deviation, variance, or the coefficient of variation, of a series of measurements [61].

3. Linearity

Linearity refers to the capability of an analytical method to generate results which are relative to the analyte concentration within a specified concentration range. The simple linear regression analysis is usually employed to evaluate the linearity over a given range. The estimated slope and its estimated variance provide a statistical
evaluation of linearity, while the estimated Y intercept can be used to assess the potential bias [61].

4. Ruggedness

The term “ruggedness” refers to the reproducibility of results obtained during the analysis of an individual sample, as variation is imposed on the conventional testing conditions. Ruggedness is thus a measure of reproducibility of assay results obtained under usual operating conditions from day to day, laboratory to laboratory, or even from analyst to analyst [60].

The purpose for this study was to validate the analytical method employed for the quantitative analysis of bromochloromethane, using gas chromatography. Validation of the analytical method was achieved by assessing the validation parameters, accuracy, precision, and ruggedness, respectively.

3.1.2. Evaluation of validation parameters

3.1.2.1 Precision and ruggedness

The validation parameters, precision and ruggedness were achieved by the preparation of a standard solution, containing bromochloromethane, dibromomethane, dichloromethane, and the internal standard - trichloromethane. The standard solution was analyzed using gas chromatography, over a period of three days to ensure that the analytical method will provide reliable and reproducible results during the experimental phase. On each day the standard solution was injected five times and the response factor, for each injection was calculated using the mass of each component weighed and the peak area obtained during integration. The response factor of an analyte equals the area of the spectral peak divided by the weight of the substance injected. Since an internal standard was used, the response factor for each analyte was determined by the ratio of the analyte area and weight to the internal standard’s area and weight as shown in equation 2.1.
Statistical evaluation of the results obtained over the period of three days, is shown in Table 3.1. The table reports the mean response factor for each component, the standard deviation, the confidence intervals, as well as the percentage error between each injection.

Table 3.1: Statistical evaluation of the response factors of a standard solution

<table>
<thead>
<tr>
<th></th>
<th>Dichloromethane</th>
<th>Bromochloromethane</th>
<th>Dibromomethane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean response factors</td>
<td>1.5861</td>
<td>1.0968</td>
<td>0.9265</td>
</tr>
<tr>
<td>SD</td>
<td>0.020206</td>
<td>0.016994</td>
<td>0.017937</td>
</tr>
<tr>
<td>t</td>
<td>2.145</td>
<td>2.145</td>
<td>2.145</td>
</tr>
<tr>
<td>LL (95%)</td>
<td>1.5749</td>
<td>1.0874</td>
<td>0.9165</td>
</tr>
<tr>
<td>UL (95%)</td>
<td>1.5973</td>
<td>1.1062</td>
<td>0.9364</td>
</tr>
<tr>
<td>Error (W/2)</td>
<td>0.0112</td>
<td>0.0094</td>
<td>0.0099</td>
</tr>
<tr>
<td>% Error</td>
<td>0.71</td>
<td>0.86</td>
<td>1.07</td>
</tr>
</tbody>
</table>

It is evident from the results obtained that the error between injections is less than 2% for each component. Thus the mean response factor for dichloromethane, bromochloromethane, and dibromomethane can be reported as 1.5861 ± 0.0112, 1.0968 ± 0.0094, and 0.9265 ± 0.0099, respectively.

To test the null hypothesis $H_0$ - There is no significant difference between the mean response factors obtained on day 1, 2, and 3- Analysis of variance (ANOVA) was used, thus comparing means obtained for components on each day. The ANOVA output, as indicated in Table 3.2, constitutes of a number of statistical variables, which includes the sum of squares for errors (SS), degree of freedom (df), mean square errors (MS), F-test statistic, P-value, and F critical value. The abovementioned variables plays a critical role in the interpretation of the results.
obtained through ANOVA analysis, thus will be briefly explained before proceeding to the results.

1. **SS** - Sum of squares for error

   The sum of the squared error gives a measure of the total error under the null hypothesis.

2. **df** - Degrees of freedom

   Each model has corresponding degrees of freedom (df) associated with it. The df for the model equals the total number of observations minus one.

3. **MS** - Mean square errors

   The mean square error is calculated by dividing the Sum of Squares with the corresponding degrees of freedom.

4. **F** - F test statistic (F = Formula)

   Is the ratio of the Model Mean Square to the Error Mean Square. The F-value provides a measure of the difference between the observed sample mean and the hypothesized mean under the null hypothesis.

5. **P** - value - Probability value

   The p-value refers to the likelihood of attaining a test statistic in close proximity to the test statistic that is actually observed. This phenomenon is based on the assumption that the null hypothesis was found to be true. Commonly, a p-value of less than 5% (0.05) is taken as sufficiently low to reject the null hypothesis. Thus, if the p-value is less than 0.05, the null hypothesis is rejected.

6. **F**- crit. - F critical value

   In most instances if the test statistic is greater than the F-critical value, the null hypothesis is usually rejected. Thus if $F > F_{crit}$, the null hypothesis is often rejected [62, 63, 64].
Table 3.2: The ANOVA output for analysis of response factors obtained for dichloromethane during the three days.

<table>
<thead>
<tr>
<th>Source of Variation</th>
<th>SS</th>
<th>df</th>
<th>MS</th>
<th>F</th>
<th>P-value</th>
<th>F crit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between Groups</td>
<td>0.0043</td>
<td>2</td>
<td>0.0021</td>
<td>18.1614</td>
<td>0.000235</td>
<td>3.88</td>
</tr>
<tr>
<td>Within Groups</td>
<td>0.0014</td>
<td>12</td>
<td>0.00011</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>0.0057</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The ANOVA output in table 3.2 indicates that there is a significant difference between the mean response factors on days 1, 2, and 3, for dichloromethane (p-value=0.000235). Thus $H_0$ is rejected.

Table 3.3: The ANOVA output for analysis of response factors obtained for bromochloromethane during the three days.

<table>
<thead>
<tr>
<th>Source of Variation</th>
<th>SS</th>
<th>df</th>
<th>MS</th>
<th>F</th>
<th>P-value</th>
<th>F crit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between Groups</td>
<td>0.0033</td>
<td>2</td>
<td>0.0016</td>
<td>24.97</td>
<td>&lt;0.00001</td>
<td>3.89</td>
</tr>
<tr>
<td>Within Groups</td>
<td>0.0008</td>
<td>12</td>
<td>&lt;0.00001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>0.0040</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The ANOVA output in table 3.3 indicates that there is a significant difference between the mean response factors on days 1, 2, and 3 for bromochloromethane. (p-value < 0.00001). Thus $H_0$ is rejected.
Table 3.4: The ANOVA output for analysis of response factors obtained for dibromomethane during the three days.

<table>
<thead>
<tr>
<th>Source of Variation</th>
<th>SS</th>
<th>df</th>
<th>MS</th>
<th>F</th>
<th>P-value</th>
<th>F crit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between Groups</td>
<td>0.0033</td>
<td>2</td>
<td>0.0016</td>
<td>35.51</td>
<td>&lt;0.00001</td>
<td>4.26</td>
</tr>
<tr>
<td>Within Groups</td>
<td>0.0004</td>
<td>9</td>
<td></td>
<td></td>
<td>&lt;0.00001</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>0.0037</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The ANOVA output in table 3.4 indicates that there is a significant difference between the response factors on days 1, 2, and 3 for dibromomethane. (p-value < 0.00001). Thus $H_0$ is rejected.

It is evident that there is a significant difference between the mean response factors calculated on each day, for all the components (p-value < 0.05). This difference between the mean response factors is clearly illustrated in Figure 3.1. Thus the response factor needed to be determined on each day before quantitatively analyzing samples. The response factor was also frequently monitored during analysis of samples by injection of the standard solution between samples.
Figure 3.1: Means graph for the response factors of dichloromethane. The bars represent 95% confidence intervals for the mean recovered masses.

The three bars do not overlap each other’s means (centre point), which indicates a high probability that the response factors calculated on the three days have significantly different means. The width of the error bars also gives an indication of the precision of the measurements. This trend is also observed for the other components, bromochloromethane as well as dibromomethane.

This graph supports the conclusion obtained from the ANOVA tables: There is a significant difference between the mean response factors obtained over the three days.

3.1.2.2 Accuracy

In order to determine the accuracy of the analytical method, three sample solutions A, B, and C, of known concentrations, were prepared and each injected 15 times
over a period of three days. The response factor that was calculated from the standard solution was used to calculate the recovery amount of dichloromethane, bromochloromethane and dibromomethane in sample A, B, and C. The error was then evaluated by using the calculated masses of the components as a percentage of the actual mass.

Table 3.5: Recovered amounts and Added amounts of dichloromethane from the recovery study.

<table>
<thead>
<tr>
<th></th>
<th>Added Amount (g)</th>
<th>Recovered Amount (g)</th>
<th>Percent Recovery (Z)</th>
<th>Absolute Bias (B)</th>
<th>Percent Bias (PB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean(n=45)</td>
<td>2.0188</td>
<td>2.0435</td>
<td>101.36</td>
<td>0.0246</td>
<td>1.36</td>
</tr>
<tr>
<td>SD</td>
<td>0.2097</td>
<td>0.1922</td>
<td>2.6424</td>
<td>0.0530</td>
<td>2.6424</td>
</tr>
<tr>
<td>t-value</td>
<td>2.015</td>
<td>2.015</td>
<td>2.015</td>
<td>2.015</td>
<td>2.015</td>
</tr>
<tr>
<td>UL (95%)</td>
<td>2.0818</td>
<td>2.1012</td>
<td>102.15</td>
<td>0.0406</td>
<td>2.15</td>
</tr>
<tr>
<td>LL (95%)</td>
<td>1.9559</td>
<td>1.9858</td>
<td>100.56</td>
<td>0.0087</td>
<td>0.56</td>
</tr>
</tbody>
</table>

Considering the evaluation of dichloromethane a total of 45 replicate injections were performed during the three days. The mean percent recovered was calculated as 101.36 %, Absolute Bias = 0.0246, percent Bias = 1.36, as shown in Table 3.5. Hence the 95 % confidence intervals for percent recovery and percent bias are given by

\[(L_z, U_z) = (100.56\%, 102.15\%),\]

\[(L_{PB}, U_{PB}) = (0.56\%, 2.15\%),\] respectively.

The 95% confidence interval for percent recovery contains 100 %; however, the 95 % confidence interval for percent bias however does not contain 0. Thus the method is slightly biased in determining the recovered amount of dichloromethane. This biased amount has to be taken in consideration when using this method of
quantitatively analyzing dichloromethane. A minimum percentage bias of 0.56 % and a maximum percentage bias of 2.15 % were obtained.

In the same manner the accuracy and percent recovery was evaluated for bromochloromethane, and dibromomethane, as illustrated in Tables 3.6 and 3.7, respectively.

Table 3.6: The recovered and added amounts of bromochloromethane, from the recovery study

<table>
<thead>
<tr>
<th></th>
<th>Added Amount (g)</th>
<th>Recovered Amount (g)</th>
<th>Percent Recovery (Z)</th>
<th>Absolute Bias (B)</th>
<th>Percent Bias (PB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (n = 45)</td>
<td>0.3884</td>
<td>0.3880</td>
<td>100.18</td>
<td>-0.0004</td>
<td>0.18</td>
</tr>
<tr>
<td>SD</td>
<td>0.1063</td>
<td>0.1039</td>
<td>2.8564</td>
<td>0.0101</td>
<td>2.8564</td>
</tr>
<tr>
<td>t-value</td>
<td>2.015</td>
<td>2.015</td>
<td>2.015</td>
<td>2.015</td>
<td>2.015</td>
</tr>
<tr>
<td>UL (95%)</td>
<td>0.3565</td>
<td>0.3568</td>
<td>99.32</td>
<td>-0.0034</td>
<td>-0.68</td>
</tr>
<tr>
<td>LL (95%)</td>
<td>0.4204</td>
<td>0.4192</td>
<td>101.04</td>
<td>0.0026</td>
<td>1.04</td>
</tr>
</tbody>
</table>

Table 3.6 which summarizes the recovered and added amounts of bromochloromethane, shows that a mean percent recovered of 100.18 % was obtained, Absolute Bias = -0.0004, and Percent Bias = 0.18 %. Hence the 95 % confidence intervals for the percent recovery and percent bias are given by:

\[(L_Z, U_Z) = (99.32 \%, 101.04 \%),\]

\[(L_{PB}, U_{PB}) = (-0.68 \%, 1.04 \%),\] respectively.

Since the 95 % confidence interval for percent recovery contains 100, or equivalently, the 95 % confidence interval for percent bias contains 0, the assay method is considered accurate and validated for bromochloromethane.
Table 3.7: The recovered and added amounts of dibromomethane, from the recovery study

<table>
<thead>
<tr>
<th></th>
<th>Added Amount (g)</th>
<th>Recovered Amount (g)</th>
<th>Percent Recovery (Z)</th>
<th>Absolute Bias (B)</th>
<th>Percent Bias (PB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (n = 30)</td>
<td>0.1914</td>
<td>0.1921</td>
<td>101.21</td>
<td>0.00069</td>
<td>1.21</td>
</tr>
<tr>
<td>SD</td>
<td>0.0661</td>
<td>0.0622</td>
<td>3.6498</td>
<td>0.0063</td>
<td>3.6498</td>
</tr>
<tr>
<td>t-value</td>
<td>2.042</td>
<td>2.042</td>
<td>2.042</td>
<td>2.042</td>
<td>2.042</td>
</tr>
<tr>
<td>UL (95%)</td>
<td>0.2160</td>
<td>0.2153</td>
<td>102.57</td>
<td>0.003038</td>
<td>2.57</td>
</tr>
<tr>
<td>LL (95%)</td>
<td>0.1668</td>
<td>0.1689</td>
<td>99.84</td>
<td>-0.00167</td>
<td>-0.16</td>
</tr>
</tbody>
</table>

From the results summarized in table 3.7, it is evident that the mean percent recovery of 101.21 % was obtained, with an absolute bias of 0.00069, percentage bias of 1.21 %. The 95 % confidence intervals for the percent recovery and percent bias for dibromomethane are given by:

\[(L_Z, U_Z) = (99.84 \%, 102.57 \%),\]

\[(L_{PB}, U_{PB}) = (-0.16 \%, 2.57 \%),\] respectively.

Since the 95 % confidence interval for percent recovery contains 100, or equivalently, the 95 % confidence interval for percent bias contains 0, the assay method is considered accurate and validated for dibromomethane.

Furthermore, two-way ANOVA were used to evaluate whether:

- The day on which analysis was performed have a significant influence on the estimated mass
- There is a significant difference between samples, and

Thus the two null hypotheses can be formulated as:
\( H_{01} \): \( \mu_{\text{day 1}} = \mu_{\text{day 2}} = \mu_{\text{day 3}} \)

\( H_{02} \): \( \mu_{\text{sample A}} = \mu_{\text{sample B}} = \mu_{\text{sample C}} \)

The two-way ANOVA output for bromochloromethane is shown in Table 3.8.

**Table 3.8: Two-way ANOVA output for bromochloromethane estimate masses.**

<table>
<thead>
<tr>
<th></th>
<th>SS</th>
<th>df</th>
<th>MS</th>
<th>F</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>6.7757</td>
<td>1</td>
<td>6.7757</td>
<td>109772.3</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Day</td>
<td>0.0012</td>
<td>2</td>
<td>0.0006</td>
<td>9.9</td>
<td>0.0004</td>
</tr>
<tr>
<td>sample</td>
<td>0.4710</td>
<td>2</td>
<td>0.2355</td>
<td>3815.4</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Error</td>
<td>0.0022</td>
<td>36</td>
<td>0.0001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

From the results obtained in Table 3.8 it is evident that there is a significant difference between the estimated masses obtained on consecutive days \((p = 0.0004)\). Thus \( H_{01} \) is rejected. All experimental samples were therefore bottled and stored in a refrigerator to reduce evaporation of the volatile components, and quantitatively analyzed using gas chromatography in the course of one day.

As expected a significant difference between the samples were obtained \((p<0.00001)\). Thus \( H_{02} \) is rejected. Any mass difference in the experimental samples will thus be detected by the system and can be quantified.

The means graph for the estimated mass, as shown in Figure 3.2, supports the conclusion obtained from the ANOVA Table 3.8.
It is evident that all three bars does not overlap each other means (centre point), which indicates a high probability that the estimated masses calculated on the three days have significantly different means. However it should be noted that the difference between the samples is much greater than the difference between the recovered amounts on each day. Figure 3.2 also clearly shows the significant difference between the mean estimate masses for each sample, thus the method can effectively be used to quantify unknown experimental samples as already mentioned earlier.

This trend was also observed for dichloromethane and dibromomethane, as shown in Tables 3.9 and 3.10.
Table 3.9: Two-way ANOVA output for dichloromethane estimated masses.

<table>
<thead>
<tr>
<th>Source</th>
<th>SS</th>
<th>df</th>
<th>MS</th>
<th>F</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>187.91</td>
<td>1</td>
<td>187.91</td>
<td>86835.33</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Day</td>
<td>0.0212</td>
<td>2</td>
<td>0.0106</td>
<td>4.89</td>
<td>0.013228</td>
</tr>
<tr>
<td>Sample</td>
<td>1.5257</td>
<td>2</td>
<td>0.7629</td>
<td>352.52</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Error</td>
<td>0.0779</td>
<td>36</td>
<td>0.0022</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3.10: Two-way ANOVA output for dibromomethane estimate masses.

<table>
<thead>
<tr>
<th>Source</th>
<th>SS</th>
<th>df</th>
<th>MS</th>
<th>F</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>1.1069</td>
<td>1</td>
<td>1.1069</td>
<td>89526.46</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Day</td>
<td>0.0003</td>
<td>2</td>
<td>0.0002</td>
<td>13.96</td>
<td>0.000095</td>
</tr>
<tr>
<td>Sample</td>
<td>0.1117</td>
<td>1</td>
<td>0.1117</td>
<td>9031.22</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Error</td>
<td>0.0003</td>
<td>24</td>
<td>0.00001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3.2 Synthesis of bromochloromethane

3.2.1 Introduction

The purpose of this investigation was to develop an optimized laboratory synthetic procedure for the synthesis of bromochloromethane in a batch pressure reactor, using phase transfer catalysis, with respect to yield.

The reactivity of reactions that is catalysed by phase transfer catalysts can be restricted by three major factors. Firstly, the distribution of the catalyst between the phases; secondly, the mass-transfer between the two phases; and lastly, the reaction kinetics in the organic phase. The distribution of the catalyst between the two phases has a direct affect on the reactivity of the whole system [65].

Since mass-transfer between the aqueous and non-aqueous phase plays a key role in the determination of the reaction kinetics and the eventual outcome of the reaction, all the factors that could possibly have an effect on the rate of mass transfer need to be considered.

During this study the effect of the following reaction variables were investigated for optimization of the phase transfer catalyzed method:

1. Reaction time
2. Amount of water
3. Temperature
4. Volume ratio of the two phases
5. Stirring rate, and
6. Catalyst concentration
3.2.2 Effect of reaction time

The effect of the reaction time on the yield of bromochloromethane was studied by performing several reactions, in which the time was varied. The reactions were carried out using benzyl triethylammonium chloride (13 mmol) as catalyst, sodium bromide (100.0 g) as metal halide, dichloromethane (265.0 g), and water (50.0 g), in a Parr 4520 bench top reactor, at a constant temperature and stirring rate of 90°C ± 1.0°C and 800 rpm, respectively. The reaction time was varied between 6 and 36 hours. At the completion of each run the reaction was allowed to cool to room temperature and the organic phase was separated from the solid sodium chloride phase. A 5 ml aliquot of the sample was pipetted into a 50 ml volumetric flask containing the internal standard, chloroform (0.375 g). The volumetric flask was made to volume with solvent, 1-pentanol, mixed until a homogenous mixture was obtained, and analyzed by gas chromatography. Table 3.11 summarizes the results obtained.

<table>
<thead>
<tr>
<th>Reaction time (h)</th>
<th>[BCM] mol.dm⁻³</th>
<th>% Yield BCM</th>
<th>% DCM converted</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>0.6169</td>
<td>15.9</td>
<td>4.9</td>
</tr>
<tr>
<td>8</td>
<td>0.7915</td>
<td>20.4</td>
<td>6.3</td>
</tr>
<tr>
<td>12</td>
<td>1.5869</td>
<td>40.9</td>
<td>12.7</td>
</tr>
<tr>
<td>18</td>
<td>2.6345</td>
<td>67.9</td>
<td>21.1</td>
</tr>
<tr>
<td>24</td>
<td>2.7276</td>
<td>70.3</td>
<td>21.9</td>
</tr>
<tr>
<td>36</td>
<td>4.1361</td>
<td>106.6</td>
<td>33.1</td>
</tr>
</tbody>
</table>

The results depicted in table 3.13 shows that as the reaction time increased, the yield of bromochloromethane increased substantially. The reaction rate is relatively slow and 106.6 % yield of bromochloromethane was obtained only after 36 hours. The percentage yield reported after 36 hours, greater than 100.0 %, may be as a
result of the highly volatile, dichloromethane, that evaporated during the transfer of sample solution from the reactor.

During the synthesis of bromochloromethane, the concentration of the reactant, dichloromethane, is in large excess. The concentration of dichloromethane thus does not change much during the reaction and can be considered as a constant. It is also evident that the rate of the reaction is independent of the concentration of any of the components. Thus, it is apparent that the synthesis of bromochloromethane, by means of quaternary ammonium salts as phase transfer catalyst, can be well described by a pseudo zero-order reaction model, which is typical for a catalyzed reaction.

\[ r_{BCM} = k[DCM] / (1 + k'[DCM]) \]

Equation 3.1: pseudo zero-order rate equation

Literature shows that in a study of reductive dehalogenation of 17 halogenated aliphatic hydrocarbons in anaerobic slurries, 15 of the aliphatic hydrocarbons studied followed pseudo first order kinetics. Interestingly, dichloromethane along with 1, 2, 3-trichloropropane were unique in that they were dehalogenated according to zero-order kinetics [66]. Zero-order kinetics is also not uncommon in phase transfer catalyzed reactions as shown in the kinetic study of the nucleophilic displacement of benzyl chloride with a bromide ion in a super critical fluid, carbon dioxide, in the presence of acetone as a co-solvent. The reaction catalyzed by 18-crown-6 followed zero-order kinetics [67]
3.2.3. Effect of water amount

Literature shows that water of hydration is essential for the extraction process by phase transfer catalysis to take place [68]. Sodium bromide (73.3g/100ml @ 20°C) is not only more soluble than the corresponding sodium chloride (35.9g/100ml @ 25°C), but in high concentrations the bromide salt forces the chloride salt to precipitate out of solution. When only a limited amount of water is present, sodium bromide will be hydrated owing to its higher affinity to water while the corresponding chlorides will remain dry and thus inert to the phase transfer exchange process. The equilibrium under these conditions is strongly shifted to the right as shown in equation 3.1., [51, 69].

Equation 3.2: Reaction of sodium bromide and dichloromethane in the presence of benzyl triethylammonium chloride (BTEAC).

\[
\text{CH}_2\text{Cl}_2 + \text{NaBr} \rightleftharpoons \text{CH}_2\text{ClBr} + \text{NaCl}
\]

However, dilution of the aqueous phase may have a considerable effect on the rate of the phase transfer catalyzed reaction as:

- It may decrease the effective rates of anion exchange and transfer,
- Increase the amount of water of hydration around an anion,
- And it may allow more catalyst to dissolve in the aqueous phase, thereby lowering the concentration of catalyst in the organic phase [69].

With the purpose of investigating the effect of water amount on the yield of bromochloromethane, several reactions were performed using different water amounts. The reactions were carried out using benzyl triethylammonium chloride (13 mmol) as catalyst, sodium bromide (100.0 g) as metal halide, dichloromethane (265.0 g), in a Parr 4520 bench top reactor. The stirring speed, temperature and
reaction time was kept constant at 800 rpm, 90°C ± 1.0°C and 6 hr, respectively. The water amount of the aqueous phase was varied between 0 ml and 100 ml. After completion of each run the reaction was allowed to cool to room temperature and the organic phase was separated from the solid sodium chloride phase. A 5 ml aliquot of the sample (organic phase) was pipetted into a 50 ml volumetric flask containing the internal standard, chloroform (0.375g). The volumetric flask was made to volume with solvent, 1-pentanol, mixed until a homogenous mixture was obtained, and analyzed by gas chromatography. Table 3.12 summarizes the results obtained.

Table 3.12: Effect of varying the amount of water.

<table>
<thead>
<tr>
<th>Water amount (ml)</th>
<th>% Yield BCM</th>
<th>% DCM converted</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>15.3</td>
<td>4.8</td>
</tr>
<tr>
<td>25</td>
<td>17.4</td>
<td>5.4</td>
</tr>
<tr>
<td>50</td>
<td>15.9</td>
<td>4.9</td>
</tr>
<tr>
<td>75</td>
<td>16.9</td>
<td>5.3</td>
</tr>
<tr>
<td>100</td>
<td>19.9</td>
<td>6.2</td>
</tr>
</tbody>
</table>

The results depicted in table 3.12 shows that as the water amount was increased from 0 ml to 100 ml, no significant change in the yield of bromochloromethane was observed. The yield of bromochloromethane varied between 15 % and 20 %. This can be ascribed to the fact that the aqueous phase was saturated with sodium bromide. Sufficient sodium bromide was added so that excess solid was present throughout the reaction. Interestingly, in the absence of water, conversion of dichloromethane to bromochloromethane is evident. Thus indicating that solid-liquid phase transfer between the metal halide and dichloromethane did occur.

3.2.4. Effect of reaction temperature

With the aim of examining the effect of varying the reaction temperature on the phase transfer catalyzed synthesis of bromochloromethane, several reactions were performed at different reaction temperatures. During these reactions benzyl
triethylammonium chloride (13 mmol) was used as catalyst, with sodium bromide (100.0 g) as metal halide, dichloromethane (265.0 g), and water (50.0 g), in a Parr 4520 bench top reactor. The stirring speed and reaction time remained constant at 800 rpm and 6 hr, respectively as the reaction temperature was varied between 80°C and 110°C. Once cooled to room temperature the organic phase was separated from the solid sodium chloride and a 5 ml aliquot of the mixture was pipetted into a 50 ml volumetric flask containing the internal standard, chloroform (0.375 g). The flask was made to volume with solvent, 1-pentanol, and shaken until a homogenous solution was obtained, and analyzed by gas chromatography. Table 3.13 summarizes the results obtained.

**Table 3.13: Effect of reaction temperature on yield of bromochloromethane**

<table>
<thead>
<tr>
<th>Temp. (°C)</th>
<th>Temp. (K)</th>
<th>1/T</th>
<th>%Yield BCM</th>
<th>% Yield DBM</th>
<th>[BCM] (mol.dm$^{-3}$)</th>
<th>k (mol.dm$^{-3}$.h$^{-1}$)</th>
<th>ln k</th>
</tr>
</thead>
<tbody>
<tr>
<td>80</td>
<td>353</td>
<td>0.00283</td>
<td>6.5</td>
<td>0.0</td>
<td>0.2522</td>
<td>0.042</td>
<td>-3.1693</td>
</tr>
<tr>
<td>90</td>
<td>363</td>
<td>0.00275</td>
<td>15.9</td>
<td>0.0</td>
<td>0.6169</td>
<td>0.1028</td>
<td>-2.2750</td>
</tr>
<tr>
<td>100</td>
<td>373</td>
<td>0.00268</td>
<td>38.4</td>
<td>0.0</td>
<td>1.4899</td>
<td>0.2483</td>
<td>-1.3931</td>
</tr>
<tr>
<td>110</td>
<td>383</td>
<td>0.00261</td>
<td>61.1</td>
<td>1.0</td>
<td>2.3707</td>
<td>0.3951</td>
<td>-0.9286</td>
</tr>
</tbody>
</table>

The results depicted in Table 3.13 show that as the reaction temperature is increased, the yield of bromochloromethane increases substantially. This increase is clearly illustrated in Figure 3.4 as the data points were best fit to a polynomial curve. This increase in yield is directly the result of the increase in the rate of anion exchange between the catalyst and metal halide to form the ion-pair (Q$^+$Br$^-$), as the reaction temperature is increased. This results in the rate of transfer of the ion-pair across the interface of the two phases to increase. However, as the temperature and the rate of the reaction increases, the selectivity to bromochloromethane decreases.
The formation of the by-product, dibromomethane, is evident at 110°C. Pitting corrosion of the stainless steel stirring shaft was also observed as the temperature is increased. Corrosion of the stainless steel reactor vessel was limited with the use of an internal glass liner. The optimum temperature, defined as the temperature at which the high selectivity is achieved at acceptable rates of bromochloromethane formation, will therefore be a compromise situation and is probably in the region of 100°C to 105°C.

![Graph](image)

**Figure 3.3: Effect of varying the reaction temperature.**

According to the Arrhenius expression the rate of many reactions (both homogeneous and heterogeneous) depends on the temperature of the reaction. Experimentally, the synthesis of bromochloromethane using phase transfer catalysis was tested to confirm if the reaction obeys the Arrhenius equation by a plot of ln k vs. 1/T, as shown in Figure 3.5.
Equation 3.3: Arrhenius equation

\[
\ln k = \ln A - \frac{E_a}{RT}
\]

Where: 
- \( k \) = Rate constant
- \( A \) = Pre-exponential factor or the frequency factor
- \( E_a \) = Activation energy
- \( R \) = Gas constant, 8.3145 J. K\(^{-1}\). mol\(^{-1}\)
- \( T \) = Temperature in Kelvin [70].

Figure 3.4: Arrhenius plot.

A plot of \( \ln k \) vs \( 1/T \) gives a straight line as illustrated in Figure 3.5, indicating that the reaction follows the behaviour described by the Arrhenius equation. The value of the activation energy \( (E_a) \) was calculated from the slope of the line \( (-E_a/R) \) as 87 kJ.mol\(^{-1}\). The activation energy of a reaction refers to the least amount of kinetic energy that reactants must possess to facilitate product formation. The relatively high
activation energy obtained signifies that the rate constant depends strongly on the temperature of the reaction.

3.2.5 Effect of varying the volume ratios of the two phases

The solvation of the ion-pair is a critical factor that dictates reactivity in phase transfer catalysed reactions. A small amount of water is extracted along with the ion-pair, thus travelling from the aqueous phase to the organic phase and can at times hinder or restrain the reaction cycle. Thus it was imperative to look into the effect the volume ratio of the two phases has on the yield of bromochloromethane. Several reactions were performed, varying the $V_{\text{organic}}/V_{\text{aqueous}}$ ratio between 0.3 and 4.0 in a Parr 4520 bench top reactor. Benzyl triethylammonium chloride (13 mmol) was used as catalyst, along with sodium bromide as metal halide (100.0 g), dichloromethane (265.0 g), and water (50.0 g). The stirring rate, temperature and reaction time was kept constant at 800 rpm, 90°C and 6 hr, respectively. At completion the mixture was allowed to cool to room temperature and the organic phase separated from the solid sodium chloride. A 5 ml aliquot of the mixture was analysed by gas chromatography, using internal standard method of quantitation. Table 3.14 summarizes the results obtained.

Table 3.14: Effect of volume ratio of two phases

<table>
<thead>
<tr>
<th>Molar ratio $(V_{\text{org}}/V_{\text{aq}})$</th>
<th>$V_{\text{org}}$ (ml)</th>
<th>$V_{\text{aq}}$ (ml)</th>
<th>Total V (ml)</th>
<th>% Yield BCM</th>
<th>% DCM converted</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3</td>
<td>62.48</td>
<td>188.46</td>
<td>250.9</td>
<td>6.4</td>
<td>2.0</td>
</tr>
<tr>
<td>0.6</td>
<td>96.35</td>
<td>154.31</td>
<td>250.7</td>
<td>7.7</td>
<td>2.4</td>
</tr>
<tr>
<td>1.1</td>
<td>129.20</td>
<td>122.17</td>
<td>251.4</td>
<td>15.1</td>
<td>4.7</td>
</tr>
<tr>
<td>1.8</td>
<td>160.89</td>
<td>90.37</td>
<td>251.3</td>
<td>27.8</td>
<td>8.6</td>
</tr>
<tr>
<td>4.0</td>
<td>201.73</td>
<td>50.32</td>
<td>252.1</td>
<td>40.9</td>
<td>12.7</td>
</tr>
</tbody>
</table>
The results clearly show that as the volume ratio of water and dichloromethane is varied from 0.3 to 4.0, the yield of bromochlormethane increased from 6.3% to 40.9%. A decrease of the volume of the aqueous phase causes the concentration of sodium bromide in the aqueous phase to increase. Therefore more $\text{Q}^+\text{Br}^-$ can be transferred to the organic phase, to accelerate the overall rate of the reaction. In this study the total volume was kept constant, thus the significant increase in the concentration of dichloromethane, (substrate), resulted in the yield of bromochloromethane to increase.

### 3.2.6 Effect of stirring rate

The reaction kinetics of phase transfer catalyzed reactions is significantly influenced by two major factors. Firstly, the rate of mass-transfer of the quaternary ammonium salt and the quaternary ammonium bromide (ion-pair) between the non-aqueous and the aqueous phase (Mass-transfer controlled or limited). Secondly, the rate of the reaction between dichloromethane and the ion-pair, occurring in the organic phase, can also influence the reaction kinetics (Chemically controlled or kinetically limited).

In most classical phase transfer catalyzed reactions the rate-limiting step is usually represented by the chemical reaction taking place in the organic phase. Chemically controlled reactions are characterised by an increase in the reactivity as the lipophilic nature of the catalyst increases, the hydration of the anionic reactants decreases, and the polarity of the non-aqueous solvent decreases. Mass-transfer controlled reactions on the other hand occur when the anion to be transported holds a high charge density and the succeeding reaction is rapid. Mass-transfer controlled reactions are characterised by:

- An increase in reactivity as the access to the charge that is present on the catalyst increases;

- Strongly dependant on agitation efficiency; and

- An increase in reactivity when polar solvents are used.[53]
It is therefore evident that the effect of stirring on a phase transfer catalysed system is directly related to the identification of the rate-limiting step. It was thus essential to study the effect of increasing stirring rate in the phase transfer catalysed reaction. Several reactions were performed in which the stirring rate was varied between 200 rpm and 1400 rpm. The temperature and reaction time remained constant for all reactions at 90°C and 6 hr, respectively. Benzyl triethylammonium chloride (13 mmol) was used as catalyst, sodium bromide (100.0 g) as metal halide, dichloromethane (265.0 g), and water (50.0 g). The mixture was then allowed to cool to room temperature at completion, and the organic phase was separated from the solid sodium chloride. A 5 ml aliquot of the mixture was analysed by gas chromatography, using internal standard method of quantitation. Table 3.15 summarizes the results obtained.

Table 3.15: Effect of varying the stirring rate

<table>
<thead>
<tr>
<th>Stirring rate (rpm)</th>
<th>%Yield BCM</th>
<th>%DCM converted</th>
</tr>
</thead>
<tbody>
<tr>
<td>207</td>
<td>15.6</td>
<td>4.9</td>
</tr>
<tr>
<td>505</td>
<td>15.4</td>
<td>4.8</td>
</tr>
<tr>
<td>603</td>
<td>16.7</td>
<td>5.2</td>
</tr>
<tr>
<td>703</td>
<td>16.3</td>
<td>5.1</td>
</tr>
<tr>
<td>801</td>
<td>14.2</td>
<td>4.4</td>
</tr>
<tr>
<td>904</td>
<td>12.9</td>
<td>4.0</td>
</tr>
<tr>
<td>1205</td>
<td>15.9</td>
<td>4.9</td>
</tr>
<tr>
<td>1403</td>
<td>15.0</td>
<td>4.7</td>
</tr>
</tbody>
</table>
The magnitude of the interfacial area that is influenced by the agitation rate, has a direct affect on the location of the extraction equilibrium of numerous anions with quaternary ammonium cations provided by the phase transfer catalyst. Thus the reaction mixture will require stirring for effective mass transfer past a minimum stirring speed in order to achieve relatively good phase contact.

The results obtained show that in varying the stirring speed between 207 rpm and 1403 rpm had no significant effect on the yield of bromochloromethane. Thus over-agitation is not required to achieve good phase contact and efficient mass transfer. In theory, if the rate determining step is solely chemically controlled, an increase in the stirring speed will show no effect or change on the overall rate of the reaction, as illustrated by the results obtained in Table 3.15. However, if the rate determining step is solely controlled by the transfer step, an increase in the stirring speed will significantly influence the overall rate of the reaction.

### 3.2.7 Effect of catalyst concentration

The effect that the catalyst concentration has on the yield of bromochloromethane was studied by performing several reactions in which the catalyst concentration was increased. The concentration of the catalyst, benzyl triethylammonium chloride, was varied between 0 mol percent and 5.36 mol percent with respect to the sodium bromide. Dichloromethane (265.0 g) and sodium bromide (100.0 g) as metal halide, dissolved in water (50.0 g), as the temperature, stirring speed, and reaction time was kept constant at 90°C, 800 rpm, and 6 hr, respectively in a Parr 4520 bench top reactor. The mixture was allowed to cool to room temperature at completion, and the organic phase was separated from the solid sodium chloride. A 5 ml aliquot of the mixture was analysed by gas chromatography, using internal standard method of quantitation. Table 3.16 summarise the results obtained.
Table 3.16: Effect of catalyst concentration on yield of bromochloromethane

<table>
<thead>
<tr>
<th>Mol% BTEAC</th>
<th>% Yield BCM</th>
<th>% DCM converted</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.7</td>
<td>0.5</td>
</tr>
<tr>
<td>0.67</td>
<td>9.3</td>
<td>2.9</td>
</tr>
<tr>
<td>1.34</td>
<td>15.9</td>
<td>4.9</td>
</tr>
<tr>
<td>2.68</td>
<td>31.6</td>
<td>9.8</td>
</tr>
<tr>
<td>5.36</td>
<td>55.3</td>
<td>17.2</td>
</tr>
</tbody>
</table>

The results obtained in Table 3.16 shows that the yield of bromochloromethane increases significantly as the concentration of the catalyst was increased. In the absence of a catalyst, halogen exchange occurred very slowly as a yield of 1.7 % bromochloromethane was obtained after a reaction time of 6 hrs. The importance of the catalyst as a vehicle to transport the bromine anions from the aqueous phase to the organic phase is clearly indicated. Figure 3.6 also shows a linear relationship between the yield of bromochloromethane and the concentration of the catalyst. Thus the rate of the reaction increases simultaneously with an increase of the catalyst concentration. As already mentioned earlier, the phase transfer catalyzed synthesis of bromochloromethane follows zero-order kinetics thus the rate of the reaction is not dependent on the concentration of the reactants but is determined by other limiting factors. The results obtained in this study thus confirm that the catalyst concentration is a limiting factor that needs to taken in account during optimization.
3.2.8. Statistical evaluation of experimental results

In our study, the effect of the individual variables was determined in the classical manner, by varying only the one of interest while keeping all others constant. A balanced experimental design (like central composite design) could not be used as correlation between certain variables was evident. A total of 26 runs were performed and the experimental data that was obtained was fit to a quadratic response surface model. The model is also capable of describing the curvatures in the response surface for the process of optimisation. Table 3.17 summarises the variables under investigation and the yield obtained for each experiment. Runs number 9, 10, and 15 were identified as the most influential “outliers”, i.e. residuals that are significantly larger than the normal (random) experimental error contained in the experiment (design), and removed from the design. It should also be noted that the effect of the catalyst concentration was not included in the model as a variable. The 26 experimental runs were performed at a fixed catalyst concentration of 1.34 mol percent benzyl triethylammonium chloride. The model thus applied to the five
independent variables, - reaction time, water amount, dichloromethane amount, stirring rate, and temperature, - at the fixed catalyst concentration.

The quadratic model after removal of all insignificant variables (\( p > 0.05 \)), was of the form:

\[
y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_5 x_5 + \beta_6 x_1^2 + \beta_7 x_5^2 + \beta_8 x_3 x_5
\]

The best fitting model contains the main effects \( x_1, x_2, x_3, \) and \( x_5 \), a single synergistic interaction between \( x_3 \) and \( x_5 \) (dichloromethane and temperature), and the quadratic terms \( x_1^2 \) and \( x_5^2 \). The stirring rate, however does not appear to be significant (\( p = 0.975 \)), this only means that stirring between 207 rpm and 1405 rpm made no difference on the yield of bromochloromethane.
Table 3.17: Experimental responses fitted to the quadratic response model:
Bromochloromethane synthesis.

<table>
<thead>
<tr>
<th>Run</th>
<th>Water (g)</th>
<th>Time (h)</th>
<th>DCM (g)</th>
<th>stirring rate (rpm)</th>
<th>Temp (°C)</th>
<th>Yield BCM (%)</th>
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The validity of the above model is exemplified by plots of the residuals obtained from using the model to predict values for all experiments carried out and subtracting these predicted values from the actual experimental values, on the normal probability scale. These residuals should be close to the straight line and scattered randomly around it, as shown in Figure 3.7. Furthermore, the variance of the residuals should be the same at all levels of the independent variables. A plot of residuals vs predicted values shows the variation in the response Y with the effect of the independent variables on the response eliminated, as depicted in Figure 3.8. 

![Figure 3.6: Normal probability plot of residuals: Bromochloromethane response surface model](image-url)
3.2.9: Profile plots

Having confirmed the statistical validity of the response surface model, the model can now be used to interpret any specific trends in the variation of the experimental responses. In order to provide a visual representation of the effect of the significant variables, the profile plots for the four variables - $x_1$, $x_2$, $x_3$, and $x_5$ - are shown in Figure 3.9 - 3.12. The profile plot shows the effect of a single variable as all other variables are kept constant.
Figure 3.8: Profile plot for water (Variable $x_1$). Reaction time: 6 hrs, Stirring rate 800 rpm, Temperature: 90°C, Dichloromethane mass: 265.0 g.

Figure 3.9: Profile plot for time (Variable $x_2$). Water amount: 50.0 g; Dichloromethane amount: 265.0 g; Stirring rate: 800 rpm; Temperature: 90°C
Figure 3.10: Profile plot for dichloromethane (Variable $x_3$). Water amount: 50.0 g; stirring rate: 800 rpm, reaction time: 24 hrs; temperature: 90°C

Figure 3.11: Profile plot for temperature (Variable $x_5$). Dichloromethane amount: 265.0 g; stirring rate: 800 rpm; reaction time: 6 hr
From the profile plots above, the following observations may be noted:

- Varying of the water amount between had no significant effect on the yield of bromochloromethane as shown in Figure 3.9

- The yield of bromochloromethane increased as the reaction time was increased, indicating that the reaction is kinetically controlled. Refer to Figure 3.10.

- Figure 3.11 show that the substrate, dichloromethane, is required to be present in an excess amount to achieve optimal results.

- The yield of bromochloromethane increased as the temperature increased as depicted in Figure 3.12.

Another important variable that also needs consideration is the concentration of the catalyst.

These observations are consistent with the following mechanistic considerations occurring during synthesis. Firstly, the quaternary ammonium halide (catalyst) that has been dissolved in the aqueous phase will undergo ion-exchange with the anion at or in close proximity to the interface. The ion-pair that is formed can now cross over the interface as a result of its lipophilic nature. In the organic phase the ion-pair is poorly solvated and nucleophilic thus nucleophilic displacement can thus occur to yield the product and a new ion-pair. The newly formed ion-pair will return to the aqueous phase. Clearly by increasing the reaction temperature, the rates of mass transfer between the aqueous and organic phase, as well as the reaction rate of nucleophilic displacement to form the product will increase. An increase in the catalyst concentration will increase the formation of the ion-pair.

In summary, the formation of bromochloromethane will be favoured by:

1. Higher reaction temperatures;
2. Higher catalyst concentrations; and
3. Excess amount of substrate
3.2.10 Optimization conditions

In order to test the conclusion drawn above with respect to the increase in yield of bromochloromethane, a single reaction was performed in which the reaction temperature and catalyst concentration were increased whilst keeping the organic: aqueous ratio (3.1:1) high, as in the method of Muthusubramanian, L. et. al., (2005). This experiment was performed in the same reactor set-up as was used for all other experimental runs however the reaction time was reduced to 6 hours. The reaction temperature and catalyst concentration were increased from 90° to 105°C, and 1.34 mol percent to 5.36 mol percent, respectively. The reaction was carried out using sodium bromide (100.05 g) as metal halide, dichloromethane (264.52 g), and water (50.25 g), while keeping the stirring rate constant at 800 rpm. The mixture was allowed to cool to room temperature at completion, and the organic phase was separated from the solid sodium chloride. A 5 ml aliquot of the mixture was analysed by gas chromatography, using internal standard method of quantitation. A 100 % yield of bromochloromethane, calculated with respect to sodium bromide, was obtained, with no indication of the by-product- dibromomethane.

The results that were obtained is probably sufficient to show that it is possible to reduce the reaction time ( for a yield in the order of 100%) significantly down from the 36 hours to 6 hours used in the above exploratory experiment.
CHAPTER 4

SUMMARY AND CONCLUSION

In this report the synthesis of bromochloromethane using phase transfer catalysis, was investigated in a batch reactor. The methodology used as base for this investigation was a published procedure by Muthusubramanian, L., et al., (2005). The experimental conditions are summarized in table 4.1.

Table 4.1: The experimental conditions reported, for the synthesis of bromochloromethane.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reaction time</td>
<td>12 – 13 hours</td>
</tr>
<tr>
<td>Temperature</td>
<td>90 °C</td>
</tr>
<tr>
<td>Sodium bromide</td>
<td>100 g (0.97 mol)</td>
</tr>
<tr>
<td>Dichloromethane</td>
<td>265.0 g (3.12 mol)</td>
</tr>
<tr>
<td>Water</td>
<td>50.0 g</td>
</tr>
<tr>
<td>Benzyltriethyl ammoniumchloride (catalyst)</td>
<td>13 mmol (1.34 mol percent )</td>
</tr>
<tr>
<td>Stirring rate</td>
<td>Not reported</td>
</tr>
<tr>
<td>Product purification</td>
<td>Fractional distillation</td>
</tr>
<tr>
<td>% Yield Bromochloromethane</td>
<td>50.0 %</td>
</tr>
</tbody>
</table>
The main objective was to optimize the reaction conditions with respect to yield and reactor throughput.

An analytical method for the quantitative analysis of bromochloromethane using gas chromatography was developed, optimized and finally validated. Validation of the GC method was achieved by assessing the following validation parameters: accuracy, precision, and the ruggedness of the method, and was carried out over a period of three days. Statistical evaluation of results obtained showed that the percentage error between injections for each component (dichloromethane, bromochloromethane, and dibromomethane) were less that 2 %. The ANOVA however showed that there were a significant difference between the response factors obtained on day 1, 2 and 3. The response factors were thus determined on each day before analysis of experimental samples and monitored during analysis.

The accuracy of the analytical method was assessed by using the percentage recovery method. During the evaluation of dichloromethane the mean percent recovered were calculated as 101.36 %, Absolute Bias = 0.0246, percent Bias = 1.36. The 95 % confidence intervals for percent recovery and percent bias are given by:

\[(L_Z, U_Z) = (100.56\%, 102.15\%),\]

\[(L_{PB}, U_{PB}) = (0.56\%, 2.15\%),\] respectively.

A minimum percentage bias of 0.56 % and a maximum percentage bias of 2.15 % were obtained. The 95% confidence interval for percent recovery contains 100 %; however, the 95 % confidence interval for percent bias however does not contain 0. Thus a slight bias in determining the recovery amount of dichloromethane is observed.

The recovery study for bromochloromethane reported a mean percent recovered of 100.18 %, Absolute Bias = -0.0004, and Percent Bias = 0.18 %. The 95 % confidence intervals for the percent recovery and percent bias are given by:

\[(L_Z, U_Z) = (99.32 \%, 101.04 \%),\]

\[(L_{PB}, U_{PB}) = (-0.68 \%, 1.04 \%),\] respectively.
Since the 95% confidence interval for percent recovery contains 100, or equivalently, the 95% confidence interval for percent bias contains 0, the assay method is considered accurate and validated for bromochloromethane.

Finally, the recovery study for dibromomethane reported a mean percent recovery of 101.21%, absolute bias of 0.00069, and percentage bias of 1.21%. The 95% confidence intervals for the percent recovery and percent bias for dibromomethane are given by:

\[(L_z, U_z) = (99.84\%, 102.57\%)
\]

\[(L_{PB}, U_{PB}) = (-0.16\%, 2.57\%)
\]

Since the 95% confidence interval for percent recovery contains 100, or equivalently, the 95% confidence interval for percent bias contains 0, the assay method is considered accurate and validated for dibromomethane.

The two-way ANOVA output for the means of the recovered amounts showed that there is a significant difference between the mean recovery amounts for all components determined over the three days. The ANOVA output verified that there is a significant difference between the three samples used in the recovery study. It should be noted that the difference between the samples are much greater than the significant difference between the mean masses determined on the consecutive days.

With the analytical method validated, the batch process could be evaluated. A total of six process variables, namely reaction time, water amount, temperature, volume of the two phases, stirring rate, and catalyst concentration, were selected for the study. The effects of the individual variables were determined in the classical manner, by varying only the one of interest while keeping all others constant. A balanced experimental design (like central composite design) could not be used as correlation between certain variables was evident. The experimental data that were obtained were fitted to a quadratic response surface model. The profile plots that were obtained from this model allowed us to provide a visual representation of the effect of the significant variables. The profile plots can also be used to predict the
effect of certain reaction conditions will have on the system and can thus be used to
determine potential areas for further studies on this system.

Interpretation of the experimental results shows that by varying the stirring rate
between 207 and 1403 rpm has no significant effect on the yield of bromochloromethane. Thus excessive stirring is not required for effective mass transfer in this system. The experimental results and the profile plots also showed that the formation of bromochloromethane is favored by:

- Increased temperature,
- Increased catalyst concentration, and
- Excess amount of substrate

Experimental results also showed that the reaction follows pseudo zero-order kinetics and that the rate of the reaction is directly proportional to the concentration of the catalyst. The reaction obeys the Arrhenius equation. The relatively high activation energy of 87 kJ mol\(^{-1}\) signifies that the rate constant is strongly dependent on the temperature of the reaction.

To confirm the effect of the selected variables for optimization a single experiment was performed. The reaction conditions are summarized in table 4.2.
### Table 4.2: Optimization conditions

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<td>Temperature</td>
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<tr>
<td>Sodium bromide</td>
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<tr>
<td>Dichloromethane</td>
<td>264.52g (3.12 mol)</td>
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<tr>
<td>Water</td>
<td>50.25 g</td>
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<tr>
<td>Benzyltriethyl ammoniumchloride (catalyst)</td>
<td>(5.36 mol percent)</td>
</tr>
<tr>
<td>Stirring rate</td>
<td>800 rpm</td>
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<tr>
<td>Product purification</td>
<td>Fractional distillation</td>
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<tr>
<td>% Yield Bromochloromethane</td>
<td>100.0 %</td>
</tr>
</tbody>
</table>

The results obtained in Table 4.2 shows that at a set temperature of 105°C, with sodium bromide (100.05 g) as metal halide, dichloromethane (264.52 g), and benzyltriethylammonium chloride (5.36 mol percent) as phase transfer catalyst, dissolved in water (50.25 g), a yield of 100.0% bromochloromethane was obtained as the stirring speed was kept constant at 800 rpm, for a period of 6 hours. The reaction system was thus improved from 50% yield of bromochloromethane after 12h to 100% yield of bromochloromethane after 6h, effectively improving both the yield and reactor throughput.

The aims and objectives to develop and validate an analytical method and to identify and study reaction variables that have a significant influence on the yield and reaction kinetics were achieved. This allowed an improved understanding as well as
modeling of the experimental data to be completed from which predictions could be made and subsequent improvements confirmed experimentally.

The results obtained shows that the null hypothesis, stating that the synthesis of bromochloromethane using phase transfer catalysis, in a batch reactor, can be optimized with respect to yield and reactor throughput, is true and can therefore be accepted.

Based on the results of this study, future work on the optimization of this reaction system would include:

- Scaling up of the laboratory scale process to industrial scale production.
- An in depth investigation into the effect of varying the catalyst and catalyst concentration
- Investigation into recovery and recycle of the catalyst and excess reactant.


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