THE DEVELOPMENT OF A COMMERCIAL PRODUCTION PROCESS FOR p-MENTHANE-3,8-DIOL

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SUMMARY

The synthesis of p-menthane-3,8-diol via the acid-catalyzed cyclization of citronellal in a dilute aqueous sulphuric acid medium was investigated using conventional batch and continuous systems in order to develop a commercial production process for said p-menthane-3,8-diol (PMD). The batch studies conducted during the first part of this study showed that the formation of PMD from citronellal occurs via an intra-molecular Prins reaction that results in the formation of both the desired PMD product, as well as the partially hydrated isopulegol. It was shown that the formation of the by-product, PMD-acetal, results from the reaction between an intermediate, 5-methyl-2-isopropylcyclohexanol, and the citronellal starting material, and not from the reaction between PMD and citronellal as previously reported. Kinetic studies confirmed the existence of a complicated kinetic model. The formation of PMD from citronellal displayed typical pseudo first order kinetics up to conversions of 70 after which the kinetic model becomes complicated as the result of the establishment of quasi equilibrium reactions between PMD and isopulegol (dehydration of PMD and hydration of isopulegol) and between PMD the PMD-acetal, both systems being acid catalysed. The PMD-acetal formation reaction appears to be second order with respect to PMD. Scale-up studies of the batch process to 30L and 50L scales showed that it would be extremely difficult to limit the level of PMD-acetal formation below the desired level of 1%, even if citronellal conversions are restricted to about 50%.

During studies conducted on a commercially available micro-structured organic synthesis plant (OSP) it was shown that it is possible to perform the PMD reaction as a continuous process. The results obtained showed that the use of a micro-mixer such as the caterpillar micro-mixer did not provide enough residence time in order for desirable conversions (≈40%) to be obtained. By combining the micro-mixer with delay-loops of different thicknesses and lengths, and using increasing reaction temperatures, it was shown that the conversion of citronellal could be improved to some extent, but compared poorly to the expected conversions for a well-stirred batch

reactor. By packing selected delay loops with inert SiC particles, improved mass transfer was observed between the organic and aqueous phases as reflected in the increased conversion of citronellal. Using the observations that were made during the use of the OSP, a continuous-flow, tubular reactor system was designed and constructed. Advanced statistical techniques were used to investigate the effect of variables such as temperature, acid concentration, reactor length, flow rate and the organic to aqueous ratio on the rate and selectivity of the reaction. Mathematical models were derived for citronellal conversion, yield of PMD and yield of PMD-acetals, and used to predict the concentrations of citronellal, PMD and PMD-acetals at set experimental conditions. The results obtained showed that it was possible to obtain a product which approached desired specifications.

Downstream processing of the PMD reaction mixture as it exits the reactor requires phase separation and neutralization of the acid catalyst solution, followed by further work-up to recover unreacted starting material and intermediates for recycle back to the synthesis reactor, followed by purification of crude PMD to the desired specification. The study showed that neutralization, prior or after phase separation, does not affect the selectivity of the PMD to such a great extent, but does influence the relative conversion due to extended contact of the catalyst with the organic phase after the reaction is terminated. Recovery of unreacted citronellal and isopulegol could be achieved by a simple vacuum evaporation step, which may either be carried out in a batch manner using traditional distillation equipment, or in a continuous process using wiped-film (short path) techniques. It was also shown that selective crystallization of PMD from the crude product mixture by addition of a solvent, such as heptanes or hexane proved to be the best way of achieving the desired product specification.

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Declaration

I declare that this thesis is my own, unaided work. It is being submitted for the degree of Doctor of Technology at the Nelson Mandela Metropolitan University, Port Elizabeth. It has not been submitted before for any degree or examination in any other Institution.

Nico Rust

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Chapter 1

Background to this Study

1.1.1. Biting Insects and disease

Biting insects such as mosquitoes, ticks, lice, and fleas carry a variety of diseases such as malaria, yellow fever, West Nile virus, Borreliosis (Lyme disease) and tick-borne encephalitis. According to statistics from the World Health Organization, approximately one person dies every thirty seconds through complications arising from these diseases globally, and one death in seventeen in the world is reported to be caused by a mosquito bite.[1] Malaria alone is responsible for between one and three million deaths every year. Mosquitoes transmit the arboviruses responsible for yellow fever, dengue hemorrhagic fever, epidemic polyarthritis, and several forms of encephalitis. Bancroftian filariasis is caused by a nematode transmitted by a mosquito bite.[2]

Malaria kills more than three million people worldwide each year. Ninety percent of the deaths reported are in Africa and seventy percent of them are children under the age of five. Although the keys to prevention, the causes, and clinical responses are well understood by societies, under-funded health care systems result in poor implementation and monitoring. As a result, patients are experiencing increasing incidents of drug and insecticide resistance. This has resulted in a malaria resurgence that has led to a more virulent disease today than in the 1960s. None of the studies that have been conducted up to date have shown that there has been a significant decline in malaria infections around the southern regions of Africa. There is also still no single cure for malaria and an effective vaccine is considered to be years away.[3]

1.1.2. Repellents

Insect repellents have become more popular amongst consumers in order to protect themselves from the dangers of being bitten by mosquitoes and other biting insects. Hence insect repellent products have developed into a very important sector of the consumer health market. However, many of the products currently available suffer from various shortcomings. Most of the commercially available products display one or more disadvantage, including the fact that they provide a limited time of protection and have to be continuously applied to remain effective; the active substances have strong odours which can lead to consumer rejection unless various fragrance materials are added in order to mask the smell of the active ingredients; active ingredients may in some cases cause harmful skin irritations, etc.[4]

1.1.3. N,N-diethyl-meta-toluamide (DEET)

Most repellents contain an active ingredient, one or more solvents and a fragrance material. After the repellent has been applied to the skin, the solvents evaporate, leaving the active material and fragrance material on the surface of the skin. This interferes with the normal scent of the body and forms “a protective layer” around the skin which repels mosquitoes.

The most common active ingredient that is used in repellents is DEET (N,N-diethyl-meta-toluamide). This active ingredient was developed by the United States army following its jungle warfare during WWII. Its mechanism of action was thought to be by blocking the olfactory receptors of insects for octen-3-ol, a volatile substance that is contained in human sweat and breath, hence blinding its senses so that the biting/feeding instincts of the insect are not triggered. However, more recent evidence has shown that DEET rather acts as an irritant to the insect, making it a true repellent.

DEET is often sold and used in concentrations of up to 100%. There is a direct correlation between the amount of DEET applied and the number of hours of

protection against mosquitoes and other insects. Despite its effectiveness, DEET suffers from a number of disadvantages, namely.[5]

- It has a high potential to irritate eyes and mucous membranes.
- The sticky, greasy skin feel and the strong, long-lasting odour lead to instinctive rejection of these products by many consumers.
- DEET-containing products are not recommended for continuous use, or for use on infant skin, being suspected of causing medical conditions such as meningitis.
- DEET has a strong solvent and plasticizer effect on many plastic items and lacquered surfaces and can cause severe damage to such user items as glasses, watches, and other synthetic materials used for clothing and accessories.
- DEET has been reported to cause severe health problems and it could even result in death in some cases,[6] although such claims have not been scientifically confirmed.

1.1.4. Natural repellents

A few natural products exist which are claimed to be effective mosquito repellents with efficacies comparable to that of DEET. Natural products commonly used include eucalyptus-based oils, lemon grass, catnip and citronellal oil.[4] The latter have been used for almost sixty years, and its mosquito repelling qualities have been verified by research. Although the repelling qualities of most of these natural products could be compared to that of DEET, it has been shown that their effectiveness only lasts, on average, up to half an hour, whereas DEET and other synthetic repellents showed 100% repellence of up to 2 hours.

1.1.5. Non-DEET synthetic products

Synthetic repellent actives other than DEET commonly used are the 2-(2-hydroxyethyl)-1-methylpropyl ester of 1-piperidinecarboxylic acid and dimethyl phthalate (or other derivatives). The latter, still being found in some repellent products, is a suspected carcinogen and may be mutagenic. The 2-(2-hydroxyethyl)-1-methylpropyl ester of 1-piperidinecarboxylic acid, also known as Bayrepel, is a relatively new active and compares well with DEET in terms of effectiveness, but suffers fewer disadvantages than DEET and is only found in Autan (Bayer) products.

1.1.6. Formulation of a novel mosquito repellent

At the beginning of 2002, the Department of Chemistry at the then Port Elizabeth Technikon recognized the growing concern related to DEET products and the drawbacks associated with their use. This led to a study which formed the basis for the formulation of a unique mosquito repellent. The basis of this study was as follows: advanced, mixture-data statistical design methods were used to identify interactions (both synergistic and antagonistic) between known active repellent compounds (only single compounds were used for this study).[7] Once the interactions between the active compounds were identified and quantified, the results were used to select the active combination that showed the highest levels of synergism. The optimum ratio of the selected actives was then determined by using a mixture optimization procedure. External efficacy tests of the synergistic mixture of repellent actives (SABS Test House) showed that this combination provided a highly effective insect repellent formulation. This formulation was subsequently further enhanced by the inclusion of a promoter substance and a slow release mechanism. Following the patenting of the said formulation in about eighty countries across the globe, the NMMU concluded an agreement with external parties to form a Joint venture company, called Afrepell Technologies Pty LTD, to commercialise products based on the novel repellent formulation.

1.1.7. p-Menthane-3,8-diol

As part of this commercialization process, the access to one of the active components, namely *para*-menthane-3,8-diol (PMD) (IUPAC name: 2-(1-hydroxy-isopropyl)-5-methylcyclohexan-1-ol) was identified as a potential hurdle as it is being produced and marketed by only one company, namely Takasago of Japan. During discussions with local representatives of Takasago, it became apparent that Takasago had limited capacity for the production of PMD (ca. 50t per annum) with the potential to increase to about 70 t per annum. Since most of Takasago's production was already being taken up by the market, the potential 20t per annum spare capacity was considered both too little to support new business based upon the new insect repellent formulation, as well as too great a risk should production problems arise.

It was therefore decided to evaluate the feasibility of producing PMD locally to support the commercialization of the novel insect repellent formulation. An initial investigation was carried out to develop a lab-scale, batch operated process. During this investigation, the potential of developing a continuous process was realised, and this is the focus of the present work.

The remainder of this introductory chapter gives a brief introduction and overview to process development, an overview of potential routes to PMD, and a brief overview of current trends with respect to the use of continuous processing in downstream chemical production. This is followed by the statement of the research hypothesis and objectives for this study.

1.2. Downstream chemical manufacturing in South Africa

Out of an estimated 80 000 types of basic or pure chemicals currently manufactured on a commercial basis world-wide, South Africa only manufactures around 300 types, or 0.4%. Most of the pure chemicals manufactured in South Africa are regarded as

commodity, low value and high volume products. However, globally, by far the majority (95% plus) of these pure chemicals are classified as fine chemicals, or "high-value low volume chemicals". These chemicals are commonly comprised of advanced intermediates, pesticides, active ingredients, vitamins, flavour and fragrance chemicals, which are produced at scales of up to 10^2-10^4 tons per annum.[8]

The fine chemical sub-sector in South Africa accounts for only 0.002% of global sales, where most other sub-sectors in South Africa produce around 0.5 to 1.0% of global output. This clearly highlights the development potential for downstream chemical production in South Africa.[8] There has been a common acceptance across government and industrial role players that the key challenge to the future growth and sustainability of the chemical industry in South Africa is to increase beneficiation in the downstream chemicals sector, which is significantly under-developed in comparison with the basic chemicals sector. As a result, the South African government and other key role players have developed a number of development and support schemes, which includes funding of tertiary institutions, to support development initiatives for the fine chemicals industry for development in this area.[8]

These factors have prompted many role players nationwide to investigate the feasibility of growing the production of high value downstream chemicals also known as fine chemicals. While it is relatively easy to identify the opportunity for fine chemicals production in order to improve growth with regards to economical aspirations, the identification of specific production opportunities is quite involved as the process which leads up to such a development is a major technical and economical exercise that can only be justified if it fills a definite need of the corporation.[9] Commonly, a fine chemical might only be recognized after various factors have been identified, thereby triggering the need for process development. In the case of chemical processes development for new fine chemical products, the development usually follows the structure shown in Figure 1.1.

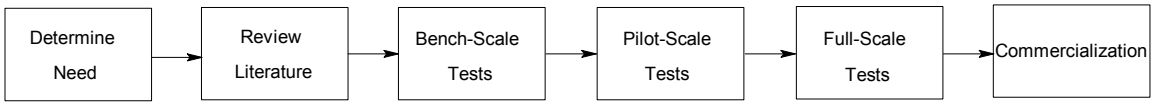


Figure 1.1: Chemical process development for fine chemicals.[10]

1.3. Determination of the need for development

Process development must start somewhere. As already mentioned, process development will only commence once various factors have been identified which indicates a need for a specific product. These needs commonly come to light as the result of:

1.3.1. Better quality products

The need for better quality products, which commonly arises as a result of persistent requests and/or complaints from customers, or from the pressures of competitors' products, often results in new process development activity. This is quite common in the chemical process industry. In many cases, a point is reached when further improvement to an existing process can no longer meet desired objectives, or development of a new product application opens the way to other market segments, thus triggering the need for a new process.[9]

1.3.2. Raw material changes

Process development might also be initiated if different raw materials become available that could have definite technical or cost advantages. The changing situation concerning raw material supply has always characterized those industrial chemical processes that start with natural raw materials, i.e., mineral ores, agricultural crops or petroleum fractions for the petrochemical industries. The situation could be

even more sensitive when the raw materials from a plant are by-products or waste products from another production plant, or main products from a plant which functions as an all year multi-purpose plant.[9]

1.3.3. Ecological pressure

We live in an ever changing world, and the demand for doing things differently, more efficiently, faster and safer always seems to be at the forefront of many new developments. This is with good reason, as we live in a day and age where we have to be aware of the consequences of pollution, global warming, etc., in order to sustain life on earth for generations to come. Therefore new chemical processes might also be the result of increasing ecological pressures from public organizations or statutory regulations set by developed countries in order to reduce the environmental damages caused by some existing chemical processes. In many situations, the solution would be to change the source or quality of the raw materials. This would require that only changes be made to the main process, whilst retaining the plant's entire infrastructure, leading to a more cost effective approach.[9]

1.3.4. Patents

Process development might also result if a company may have been prevented from entering into a specific production line that was well protected by an existing patent, which could either cover the nature (analysis, specification) of the product or a specific production process for such products. If the patent covers only the nature of the product, a process development effort would be required as soon as it is established that such a patent would expire soon, or if a way to by-pass such protection can be proposed (e.g., a small change in the formulation that does not affect the performance). The patent law only prevents the selling of the product covered by the patent, not the study or the preparation for its eventual production or production for storage.[9]

1.3.5. Newly available technologies

New industrial technologies which become available from external sources which are supplying other industries might also prompt opportunities for new process developments. Such new technologies could be applied to the potentially profitable production of desired products, which previously could not be produced economically. The timely recognition and exploration of such opportunity is one of the main challenges of industrial research and development.

1.3.6. New functions

A new product could also be needed to fill a new function at the users end resulting from some parallel technological development in other industries. If the need for such a product can be defined, a process development effort will be justified.[9]

1.4. Driving forces for process development

The development and implementation of any new process is very expensive and therefore requires significant investments in terms of time and money. It is therefore necessary that a process development activity be backed by a large organization; it could be a commercial or an academic institution. Another driving force which is also necessary is the actual promoters of the project. These promoters most commonly consist of individual scientists, an academic department, an industrial research organization, or an engineering company. These promoters often form part of the initial process development which includes elements such as[9]:

- The invention with its justification, its basic chemistry and mode of operation and its implementation logic.
- A basis for the formal claims for a patent application, which could be derived from a novel way of reasoning or newly discovered factual evidence.

- A bench scale experimental demonstration of the novel aspects of the proposal, which will motivate the development of such a process.
- The promoting of a project, i.e., raising the interest of corporations, raising funding, etc.

The second part of any process development follows the transfer of the management and the associated responsibility of the project to a larger corporation for commercialization. This is obvious as the promoters, which are generally part of a small group of people, do not have the means, nor do they have the time and possibly the ability to pursue, in detail, all of the possible options.

1.5. The process initiative

Research and development activities are often the start of new process development efforts; for example, R&D may lead to a better understanding of the limitations of an existing industrial process. The new data developed often triggers or seeds the notion which leads to finding a better way of doing things and thus the start of developing a process. However, a new process might not always start at the research and development activities, as it could also be an innovation which forms part of the personal motivation of a researcher or development scientist, which is often linked to a financial bonus or an incentive of some sort. These rewards are often used in large companies to function as incentives in order to generate new ideas and the start of process development.[9]

The process idea might also be formed by conducting literature reviews before any process development efforts are made, as this will most commonly form the basis of any future developments. These literature reviews could in fact stimulate a better understanding of future concepts regarding products and also prohibit the development of processes which are already known, thereby saving valuable time/money.

1.6. Initial work

Most commonly, after it has been shown that the review of a process corresponds to a “real” need, the go ahead for the process will be given. This will be followed by experimental work which will generally consist of the process definition, feasibility tests and some laboratory work. In such an instance the “would be” process will be reviewed by doing some literature reviews and providing a concrete, possibly optimistic, illustration of the implementation of the concept, if it could be made to work as intended.

In the initial stages, the process will be defined using block diagrams whereby the process will be broken down into blocks or sections of the process which will, as far as possible, describe only one well-defined operation. This will allow for a visualization of the process and also allow one to see the bigger picture concerning the process. Mistakes not previously noted might be identified during this stage and save a lot of time. A simple illustration is shown below:

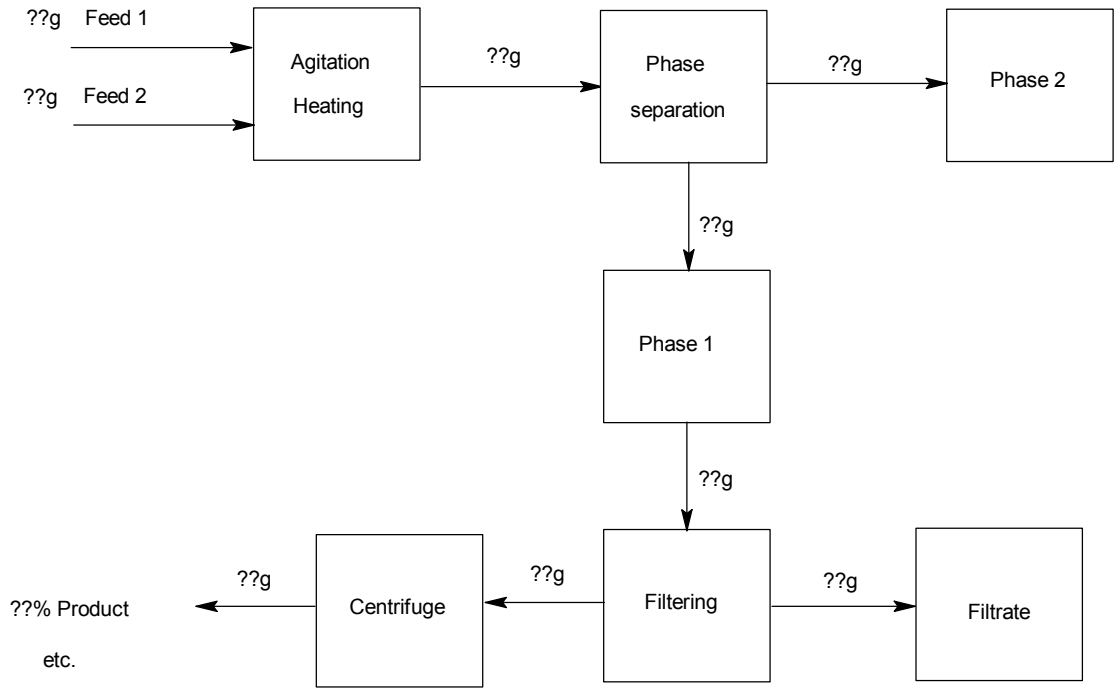


Figure 1.2: Simple representation of a block diagram

Each of these blocks would represent operations such as the running of a chemical reaction, heat/mass transfer operations, separation, or material handling or storage, to name but a few examples. For each one of these unit operations, the aim for each operation should be clearly defined using quantitative means, such as minimum concentrations, composition of the exiting streams, minimum recovery of a product, etc. At this stage, these definitions will largely depend on assumptions and on previous professional experience. After the process has been schematically shown to be a valid approach to the new process, the experimental work will be started.[9]

1.6.1. Laboratory scale

The main purpose of the experimental work done in the lab during the development stage is the collection, the correlation and the presentation of the design data that is specifically needed for the design and optimization of the new process.[9] However, it is generally known that in any process, the optimum results cannot be obtained during these first attempts, but should be achieved later on during specific optimization activities. Laboratory demonstrations can have severe limitations as they are performed at a scale which is not a true reflection of the commercialized process; for example, they use standard or improvised laboratory equipment and are performed using laboratory reagents.

1.6.2. Optimization

The process optimization goals of any development effort might change during the development from laboratory through scale-up to dedicated manufacturing systems. However, most commonly the initial goal of any process would be to optimize the conversion of a reaction in order to generate the maximum yield of isolated product.[11] This general order of optimization may differ according to the nature of the process. Once the in-process yield has been optimized and the maximum amount of isolated product is obtained, one would start “tweaking” the process to minimize impurities as

the presence of impurities can complicate purifications and decrease isolated yields further downstream. Furthermore, impurities that are difficult to remove are particularly costly in the production of any fine chemical, and thus it would be the goal to prevent impurities rather than to "cure" unsatisfactory products.

A chemist's intuition is usually a first resort in optimizing any reaction; however, when intuition fails, one would resort to other methods of optimizing the process in a reasonable amount of time. Common methods for the optimization of chemical processes may involve the use of investigations where one variable at a time is modified (the OVAT approach). This may cause the investigator to ignore potential optimizations from inter-dependent variables which could result in incorrect conclusions. Therefore one would rather consider more organized approaches: for example, the use of statistical design of experiments or DOE's.[11] DOE's will be discussed in detail further on in this thesis.

1.6.3. Product refinement

Most chemical processes require further treatment of the reaction mixture after the reaction has been completed. These treatments, commonly referred to as product work-ups or downstream processing (DSP), will be applied to processes and will include steps such as quenching of the reaction to stop it, providing safe conditions for personnel to continue processing, removing impurities, providing the product in a form convenient for purification, or safely neutralizing waste streams. The best work-up for any process would be a work-up that includes the fewest number of steps, the smallest number of vessels, the minimal number of extractions and the minimal amount of solvent needed for extractions.[11] This particular part of process development can be studied during the bench scale tests or even be investigated once the process has reached the pilot scale.

1.6.4. Pilot scale

After it has been demonstrated that a process can be successfully performed in small scale laboratory equipment, it will be necessary to scale up the process to the pilot scale. The jump from bench to pilot plant will usually be the single largest numerical increase in scale (up to 100 times) that the fledgling process will ever experience and can present the greatest challenges. This step-up is commonly used to demonstrate that the technology works and that the process can be successfully scaled up for the production of kilogram quantities of product. Product so produced is typically used by various organizations for initial testing and screening experiments.

During the first stages of pilot plant production, a trial run might be performed where the conditions that were used in the laboratory is applied directly to the larger equipment. This process can be helpful in identifying potential scale-up issues that may require engineering assistance or special equipment to handle, help to identify rate limiting steps, and give a feel for the overall feasibility of the process.[12]

1.7. Route selection

In the trial experiments, which includes the lab work, expedient routes are often followed in order to expedite the production of small quantities of the product for initial testing. These routes often change when the process reaches the production stage as the key aim of the research investigations are to develop a practical route in order to make larger quantities of a specific product. These routes are commonly defined by factors as highlighted below.[13]

1.7.1. Probability of success

This factor is usually hard to asses at the initial stages of product development, but it usually runs hand in hand with well known chemistry. Reactions that are well

documented with a wide range of analogous compounds giving similar results are usually preferred.

1.7.2. Starting materials

Most compounds that are listed in standard laboratory catalogues are generally only available in laboratory quantities. This would not work at a commercial level as the manufacturing syntheses would require that materials are available in bulk and at reasonable cost.

1.7.3. Safety

Safety is vital in any production facility, especially where large-scale reactions are performed. Most reagents exhibit some degree of toxicity, and large-scale equipment is designed to give a good level of containment to protect the operators and environment. Potentially explosive reactions, however, cannot be handled safely in conventional equipment and would require that further levels of containment be made. This needs to be considered for scale-up of such reactions.

1.7.4. Environment

The safe containment of reactants and disposal of waste is of very high importance when selecting a chemical synthesis route. The production of waste always has a price tag to it and could, in some cases, increase the production costs of any fine chemical exponentially. What is very disturbing is that many of the wastes that will be produced will not be treated properly and merely sealed into containers which will be buried in shallow dump sites. This might have a huge impact on the environment as some of these containers could, in fact, start to leak during an earthquake or catastrophic event, and contaminate groundwater systems bound for future usage by humans. The route which produces less chemical waste is therefore desired.

1.7.5. Catalysis

Reactions that make use of catalysts are generally more desirable than reactions that use stoichiometric amounts of auxiliary reagents since the latter generates a stoichiometric amount of waste products, and waste products, require safe and often expensive disposal. However, during the early development stages of a new product, the likely use of a specific catalyst, apart from the standard documented catalytic reactions, will not be known. While the potential benefits of catalysis are enormous, the time taken to devise a catalyst for a relevant synthesis can be prohibitive.

1.7.6. Number of steps

Routes with the fewer steps are preferred over alternative routes having more steps, and the potential to reduce the number of steps in a synthetic sequence by only one step can often be enough justification for a new process development exercise. Fewer reaction steps favour higher overall reaction yields, decreases the risk of potential hazards, minimizes the amount of waste produced, and reduces plant occupation.

1.7.7. Yield

A synthesis which generates high yields generates fewer impurities and generally leads to easier work-ups. It also offers the possibility of telescoping reactions, which is a procedure whereby the product of a chemical reaction is not isolated and purified, but is used directly in the next stage of the synthesis.

1.7.8. Equipment

Equipment can also play a vital role in deciding which route to take. In the early stages of process development, one might consider whether the reaction can be

performed in a multi-purpose standard plant or if special equipment is needed to perform the reaction. Special equipment might lead to a cleaner process being run, but in the early stages of any process these types of equipment might not be available. However, the purchase of special equipment, which results in large capital expenditures, will only be justified once the product has proven its value and one has gained enough confidence that it will work.

1.7.9. Convergent route

Convergent synthesis is usually very desirable as it permits the simultaneous production of separate fragments of the final molecule in different units before joining them together at the final stage. In general, these routes are overall more efficient than a linear synthesis having the same number of stages and the same yields per stage.

1.7.10. Robustness

Reaction routes which are tolerant of a wide range of conditions, e.g., concentration, time and temperature, to name but a few, are more likely to be successful on a large scale than reactions involving unstable intermediates or requiring critically defined narrow operating conditions.

1.8. Conventional chemical processes

The fine chemical, agrochemical, and active pharmaceutical ingredient (API) production sector generally relies essentially on batch or semi-batch process technologies. Such facilities are usually managed in so-called production campaigns and are typically operated using “train” approaches where reaction and work-up steps are fundamental unit operations of such processes. Advantages commonly

associated with batch and semi-batch processes over their continuous counterparts are their flexibility and versatility with regards to greatly varying reaction kinetics. Such vessels can accommodate various phases (solid-liquid-gas), as well as various downstream operations such as distillation, liquid-liquid extraction, and crystallization with great ease. In addition, the relatively small production volumes generally required, as well as the often short lifetime of products, give such multi-purpose facilities a distinct capital investment advantage over dedicated continuous production plants. The latter are, however, significantly better suited and more economical for the production of bulk, or commodity chemicals.

1.9. Scale-up

The major disadvantages associated with batch reactors relates to the scaling-up of such reactions or reactors. Under normal circumstances, small quantities of compounds can easily be produced in laboratory glassware or by using large glass vessels in sizes of up to 100L. Using this approach, even 1 - 5 kilograms of product could be produced in most cases. However, when larger quantities of material are required, the scale-up of such processes generally becomes necessary due to one or more of several reasons:

- To provide samples of product/waste etc., for further testing;
- To demonstrate the technology;
- To confirm material and energy balances;
- To evaluate the performance of unit operations required on a larger scale;
- To gain further information for the design of larger equipment; and
- To produce commercial quantities of product for market development/penetration.

The scaling up from laboratory glassware to larger reactor vessels is not a straightforward process.[12] There are a number of things that may not be instantaneously noticeable to the ordinary laboratory scientist, and some of these

factors may have a tremendous impact on process performance. The most common factors that plague the scale up of such processes are discussed below.

1.9.1. Reactor size

Certain constraints become apparent when deciding to produce larger quantities of material by using larger vessels. For example, glass vessels are relatively weak and this limits the amount (mass) of material that can be supported in larger scale vessels. They are also prone to cracking during heating and cooling operations. This particular problem is often solved by fabricating reactors out of steel and coating them with a thin layer of glass to provide for structural strength, and to confer chemical inertness equivalent to laboratory equipment. Other limitations are commonly related to the mere size and also the setup of such vessels as they cannot be interchanged at will to perform other reactions which require different settings. The size of the reactor also determines the minimum volume of reaction mixture which is needed to ensure effective mixing during a reaction.[13]

1.9.2. Expanded time scale

Unit operations such as distillations, heating/cooling, separations etc., which usually take a few minutes in the laboratory, can take several hours or more in scaled-up vessels as the rates at which chemical and physical phenomena such as mixing, reaction, filling, etc., occurs are generally slower as the result of their mere size, heat transfer and mixing capabilities. These extended time scales could be detrimental to heat or time sensitive products during a process.

1.9.3. Heat transfer and temperature control

Heat transfer is a critical factor in all chemical reactions, irrespective of whether heat transfer is required to raise the temperature of the reagents, or to keep the reaction

mixture at a constant temperature in order to obtain suitable selectivity and kinetics for a given system. Generally, reaction temperatures can be controlled easily in small laboratory vessels due to their very high surface area to volume ratios. This is, however, not true for very large reaction vessels, especially vessels in the 1000L scales.[12,14]

While not all reactor vessels are spherical, the impact of increasing size on the surface area to volume ratio may easily be illustrated by plotting the ratio

$$\frac{A}{V} = \frac{4\pi r^2}{4\pi r^3 / 3}$$

as a function of increasing volume, as illustrated in Figure 1.3.

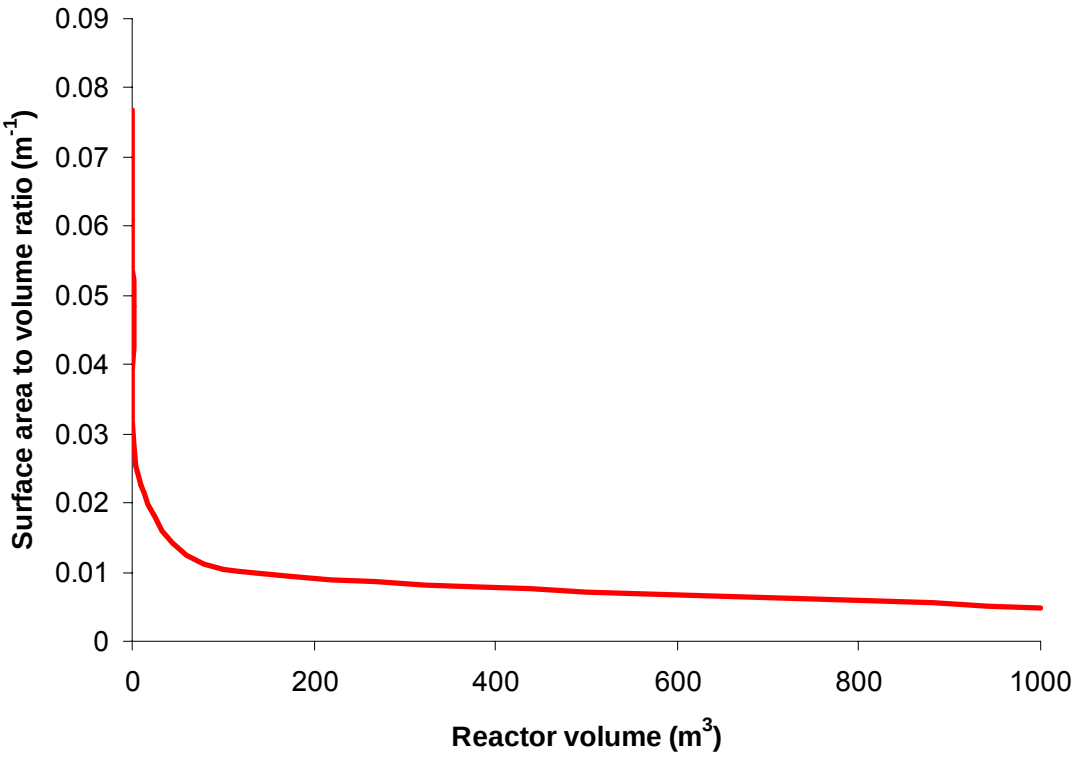


Figure 1.3: Surface area to volume ratio with increasing reactor size

Heat transfer is commonly achieved by the circulation of heat transfer liquids through a jacketed vessel,[13] or an internal or external heat exchanger in order to obtain the desired heat transfer. The rate of heat transfer ($Q/t = U.A.\Delta T$) is a function of the thermal conductivity of the vessel wall, the heat transfer coefficients for the liquid surface films on the reactant and jacket/heat exchanger side of the vessel wall, the temperature difference between the heat transfer fluid and reaction mixture, and the available surface area across which heat transfer can occur. The heat transfer coefficients for reaction mixtures and heat transfer fluids are influenced by the physical properties of the reaction mixture or heat transfer fluid, as well as the rates of agitation thereof. Heat transfer can generally be improved by better agitation and increasing the temperature difference between the heat transfer liquid and the reaction mixture.

Nevertheless, the removal or addition of heat to reactors with increasing size during or after reactions becomes increasingly more difficult, and removal rates can be up to 10 times and even as much as 30 times slower at commercial scale per unit volume. This implies that the time scale required to remove/add heat to commercial scale reactors will be substantially longer than traditional lab equipment, and this aspect will require careful consideration by the process chemist and design engineers.[12]

1.9.4. Reactor mixing and mass transfer

When two reactants in two different phases are reacted, at least one of them has to be transported to the other phase in order for a chemical reaction to occur. This process of transport between phases is known as mass-transfer and is, as in the case of flowing fluids, the result of the combined effects of diffusion and convection. If fluids are well mixed, the mass transfer may be considered to take place in a thin layer close to the interface. Although the concentrations of the components in the bulk are practically equalized, large concentration gradients may exist in the diffusion layer adjacent to the phases.[12,14]

Mass transfer, in general, is a function of the degree of mixing, and influences the reaction rate of many chemical processes. This is often very noticeable when scaling up a process, and the conversion is lower in larger vessels for a specified unit time. These processes are deemed to be mass transfer limited, and mixing becomes crucial to achieve acceptable yields and cycle times.

1.10. Production of p-menthane-3,8-diol

1.10.1. Routes to p-menthane-3,8-diol

Many potential routes exist for the synthesis of PMD. This includes routes from a variety of different starting materials, as well as routes using the same starting materials, but with different reaction approaches. In order to meet the quality and price specifications (see later) for the desired product and to ensure that the most economically and technically viable method is selected, all the possible routes should first be examined. In the present case, route selection has essentially been done previously[15] and only a brief overview of the potential routes will be given.

1.10.2. Extraction or isolation from naturally-occurring oils

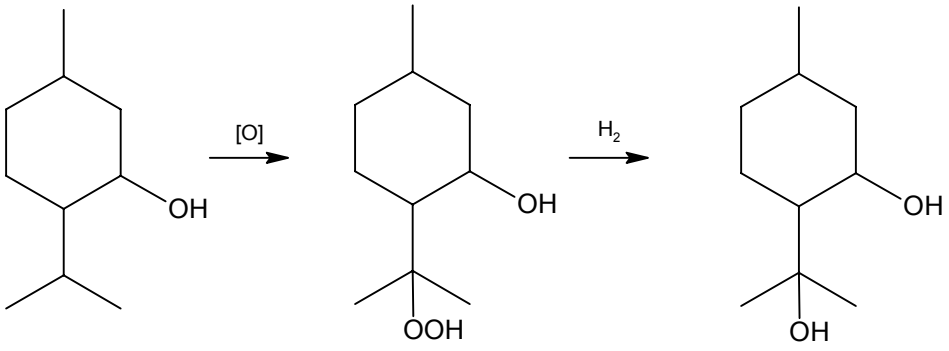
p-Menthane-3,8-diols, which are known to exert a repellent effect on insects such as mosquitoes and fleas, are one of a series of naturally-occurring compounds obtained from the leaves of Eucalyptus citriodora trees. Eucalyptus citriodora is a genus of trees and shrubs in the family Myrtaceae that originated in Australia, but now commonly grows in almost all tropical and subtropical areas. Eucalyptus trees are characterized by vertically hanging, white, leathery leaves and ragged bark. There are close to 600 species of eucalyptus, one of which is Eucalyptus citriodora Hook. E. citriodora is also known as citron-scented gum, lemon eucalyptus, lemon-scented gum, Corymbia citriodora, and spotted gum. Various extracts from the leaves and bark of E. citriodora has been credited with anti-inflammatory, antibacterial, and

antifungal activity and, recently, the extract from its leaves has gained popularity as an insect repellent.

E. citriodora leaves contain many compounds with pesticide activity including aromadendrene, citronellal, citronellic acid, citronellol, citronellyl acetate, p-cymene, limonene, linalool, alpha-pinene, *p*-menthane-3,8-diol, tannin, terpinene, terpinolene and ursolic acid. Of the compounds contained in the leaf extracts of E. citriodora, *p*-menthane-3,8-diols have been identified as the compounds that provide the most noticeable insect repellence action. It is also of interest to note that the leaf extracts of E. citriodora also contains citronellol, which is the active ingredient in oil of citronella products but which has a rather poor efficacy in repelling biting insects. Oil of citronella, however, is not obtained from E. citriodora, but rather from perennial grasses indigenous to tropical Asia (C. nardus and C. winterianus).[16]

1.10.3. Synthesis of p-menthane-3,8-diol from menthol

p-Menthane-3,8-diols can potentially be prepared from menthol, an important ingredient of various cosmetics, pharmaceuticals, toothpastes and other specialty products, by selective oxidation to form the hydroperoxide molecule (Scheme 1.1). Reduction of the hydroperoxide results in the formation of *p*-menthane-3,8-diol. While this route appears technically viable, the high cost of menthol will render this approach economically unviable.

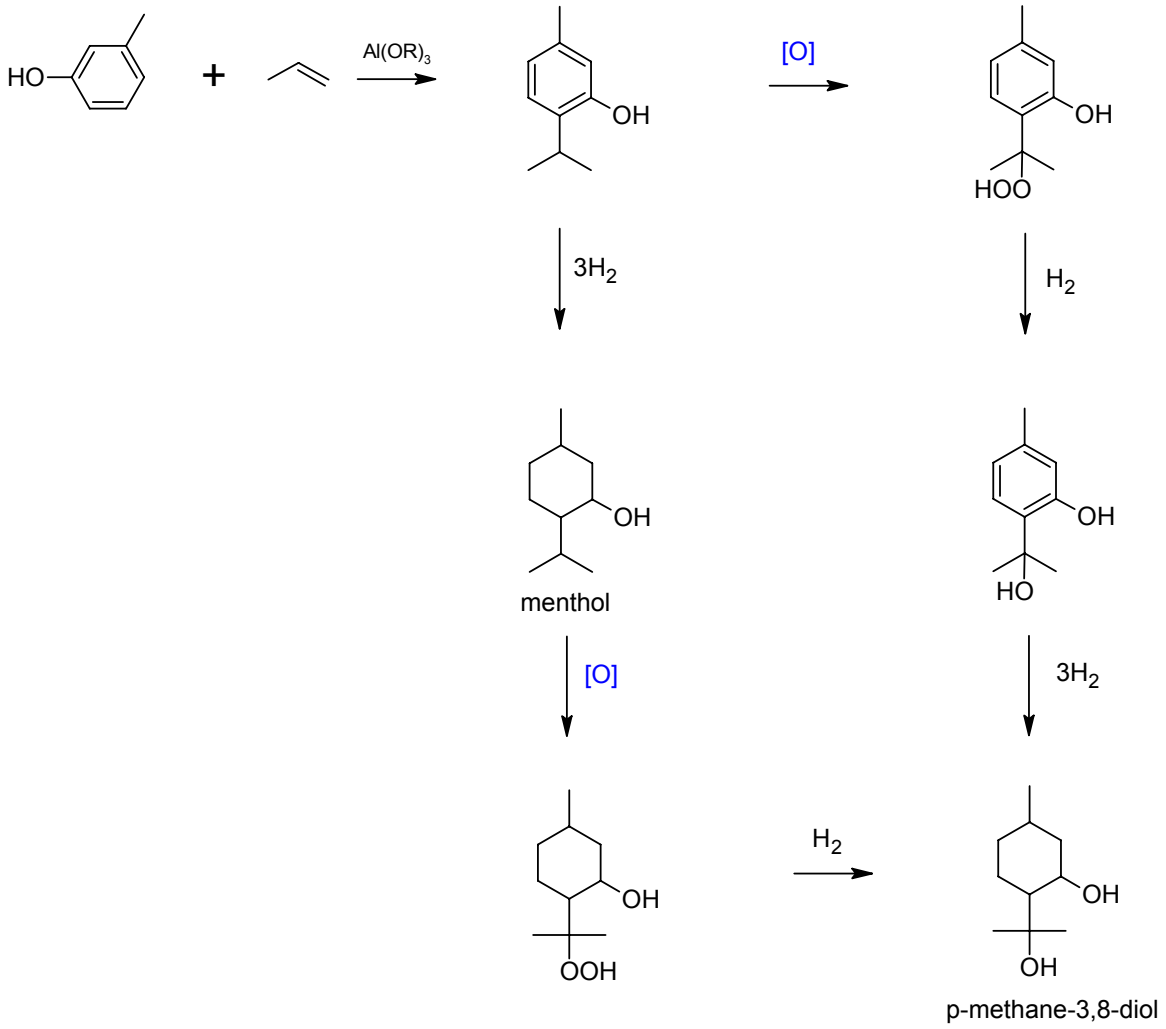


Scheme 1.1: Synthesis of PMD from menthol

1.10.4. Synthesis of p-menthane-3,8-diol from m-cresol/thymol

p-Menthane-3,8-diols may be produced from m-cresol according to the general synthetic scheme shown in Scheme 1.2. This type of synthesis requires the alkylation of m-cresol with propene using an alkoxide (or other) catalyst ($Al(OR)_3$) to produce thymol.[17] Thymol (2-isopropyl-5-methylphenol) is an aroma chemical used in flavour, fragrance, and personal care products and has antiseptic, antiparasitic, and anti fungicidal properties. In addition, it is also an advanced intermediate in the production of menthol. The use of the very active aluminium alkoxide catalysts allows these reactions to proceed at a high rate which favours the 5-methyl-2-isopropylphenol isomer over the 3-methyl-2-isopropylphenol isomer.

Alternatively, the thymol can be produced over zeolite catalysts, but it is not clear whether this approach is followed in any existing commercial process. This process, which was developed by the CSIR in conjunction with the University of Cape Town's catalysis research unit (UCT), involves shape selective zeolite catalysis to convert m-cresol to thymol.[18] Thus thymol may be synthesized via isopropylation of m-cresol, which is produced as co-product using the CSIR`s



Scheme 1.2: Synthesis of *p*-menthane-3,8-diol from P-cresol/thymol

SAFOX™ technology along with *p*-hydroxybenzaldehyde during the catalytic air oxidation of a mixed p-/m-cresol stream.

The isopropylation of m-cresol can give products with an isopropyl group in the 2-, 4-, and/or 6 positions.[19,20,21] Since the thymol molecule (5-methyl-2-isopropylphenol) is stereochemically the “slimmest” of the possible isomers, it is the predominant product when using medium pore zeolites. The use zeolites during this process allows stable catalyst operation at high yields, and a selectivity of around 90% towards thymol is claimed.

The second part of the process involves the catalytic air oxidation of thymol to form the thymol hydroperoxide in a manner similar to the production of cumene or cymene hydroperoxides.[22,23,24] This oxidation, like in the case of the cymene hydroperoxide process, may suffer selectivity problems as a result of:

1. The presence of the methyl group on the aromatic ring which may also undergo oxidation to give the primary hyroperoxide,[25] and
2. The formation of the primary hydroperoxide which can severely reduce the selectivity of the oxidation process since the primary hydroperoxide can decompose, for example by acid catalysis, to form formaldehyde, which binds with thymol to form resins in a ratio of one formaldehyde to two thymol molecules.[26,27,28]

While the extent of oxidation of the methyl group (formation of the primary hydroperoxide) will not be large in view of the relative reactivity of tertiary vs primary hydrogen, the condensation of formaldehyde with the free phenolic group of thymol may be more problematic and may even require protection of the phenolic group in order to achieve reasonable yields of product.

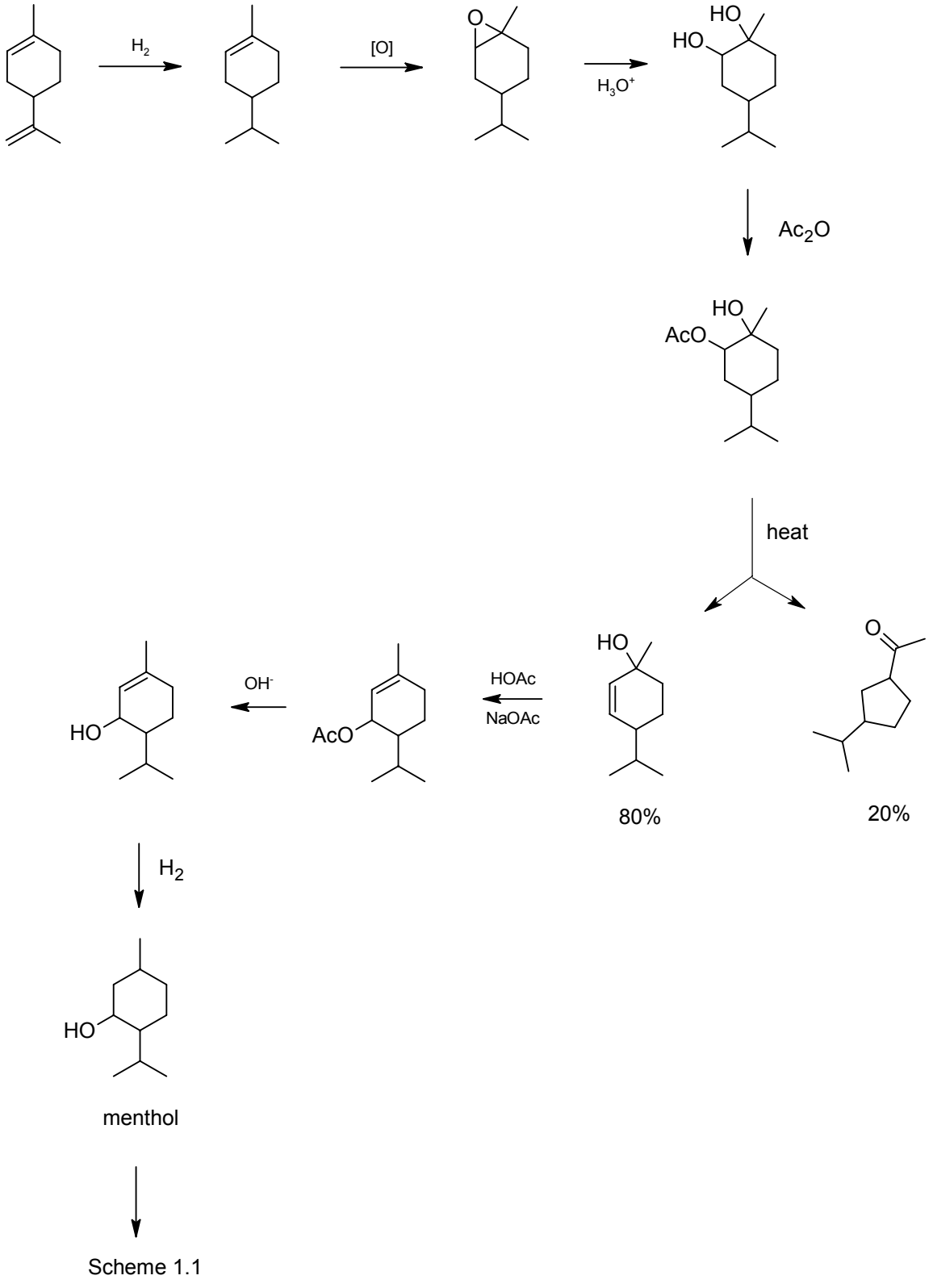
Alternatively, the initially produced thymol may first be converted to a racemic mixture of menthol isomers, which may then be converted to p-menthane-3,8-diol by hydroperoxidation and reduction.[27] This route appears more feasible since the problematic condensation reaction between the free phenolic group of thymol and formaldehyde which only forms from the cresol is circumvented. The ratio of tertiary vs. primary hydroperoxide formation is not expected to differ substantially from the thymol oxidation route.

1.10.5. Synthesis of p-menthane-3,8-diol from limonene

Limonene is a terpene, derived from steam distilling orange and lemon peels.[28] Limonene of high optical purity can be hydrogenated to 1-menthene over a Raney-Ni

catalyst (~97% yield). Epoxidation of the hydrogenated limonene gives 1-menthene epoxides, which on hydrolysis yields mainly hydroxyneocarvomenthol (Scheme 1.3). The latter is then acetylated to hydroxyneocarvomenthyl acetate after which it is pyrolized to form a mixture of eight parts of trans-2-menthene-l-ol and two parts of a ring contraction product, 3-isopropylcyclopentyl methyl ketone.

At this stage, the products can be purified but it is more practical on a large scale to subject the crude mixture to solvolysis in acetic acid/sodium acetate, wherein the 2-menthene-1-ol is converted to a mixture of the perityl acetates through allylic substitution-rearrangement (mixture of isomers). These isomers can be separated with difficulty using fractional distillation; however, using the crude mixture would be more convenient. The crude mixture is hydrolyzed with base to give the corresponding mixed cis- and trans-piperitols, which are easily separated by distillations along with the 3-isopropylcyclopentyl methyl ketone formed during the pyrolysis step. These piperitols are selectively hydrogenated to form a mixture of menthol isomers. Once menthol is produced, it can be oxidized and thereafter reduced again to form p-menthane-3,8-diol (Scheme 1.1).



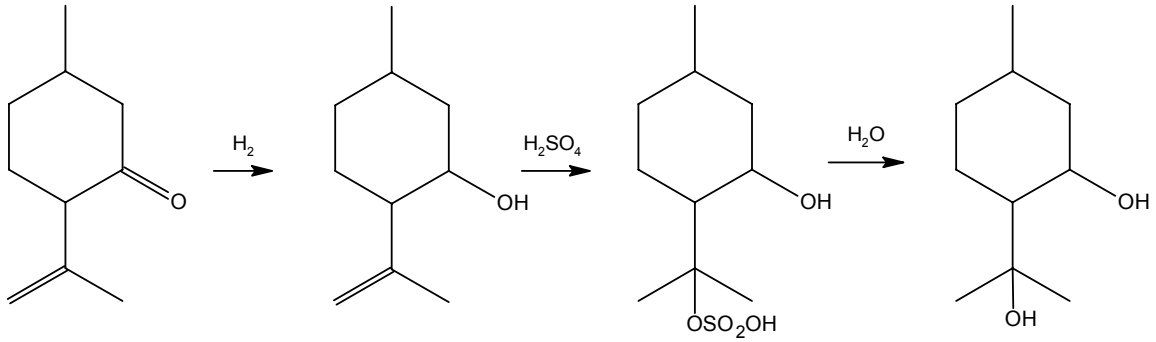
Scheme 1.1

Scheme 1.3: Synthesis of p-menthane-3,8-diol using limonene as starting material

1.10.6. Synthesis of p-menthane-3,8-diol from pulegone

Pulegone is a naturally-occurring organic compound which is commonly found in essential oils from fresh leaves of Mentha piperita L., Mentha longifolia L. Huds., Mentha pulegium L., Mentha sylvestris L., Calamintha incána (Sm.) Heldr., and Micromeria fruticosa L. Pulegone has a pleasant odour similar to peppermint and camphor. It is used in flavouring agents, in perfumery, and in aromatherapy.[29,30]

For the p-menthane-3,8-diol synthesis from pulegone, the ketone group in pulegone is reduced to the secondary alcohol of isopulegol. This reduction can be carried out using a wide variety of hydrogenating agents such as $LiAlH_4$ or $NaBH_4$ or molecular hydrogen in the presence of noble metal catalysts[31,32] as shown in Scheme 1.4.



Scheme 1.4: Synthesis of p-Menthane-3.8-diol from pulegone

Following the reduction step, the isopulegol double bond is then hydrated by treatment with water and an acid catalyst, preferably sulphuric acid. Other acids such as nitric acid or perchloric acid can also be used. The bisulphate or other salt is then hydrolyzed to the tertiary alcohol of p-menthane-3,8-diol.

1.10.7. Synthesis of p-menthane-3,8-diol from citronellal

1.10.7.1. Synthesis of citronellal

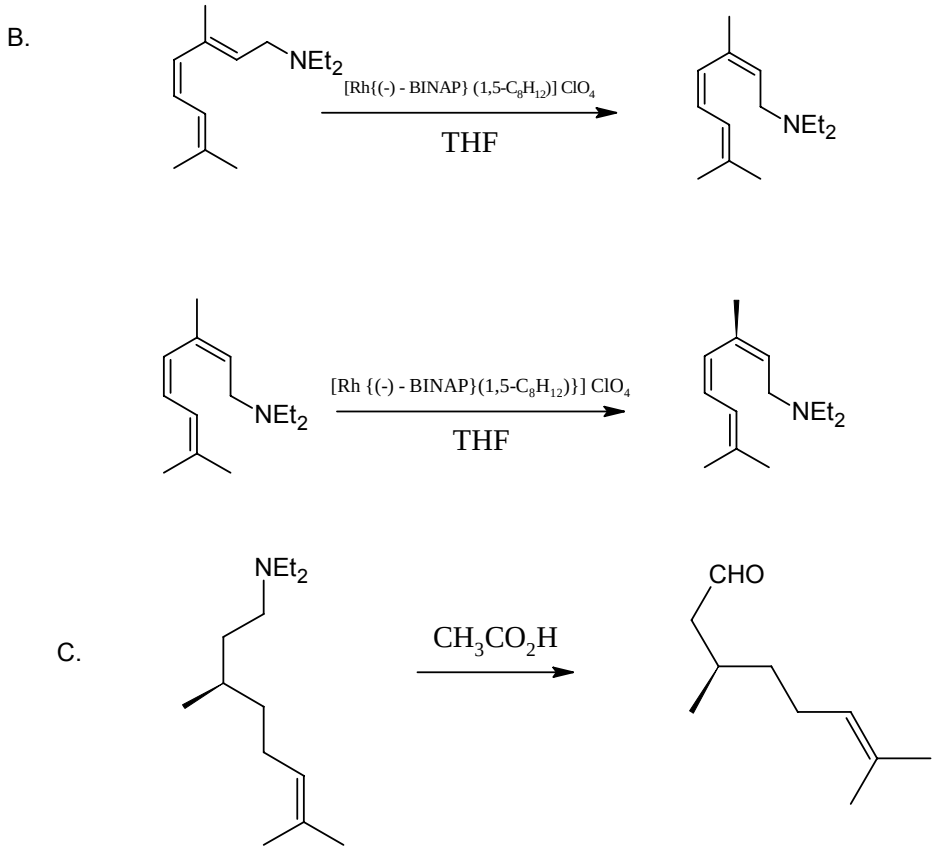
Citronellal is a mono-terpene, predominantly formed by the secondary metabolism of plants. It's also found in more than 50 essential oils.[33] Besides its use as an important commodity in the fragrance industry, citronellal is employed as an intermediate in the synthesis of several commercially important compounds. Citronellal along with citral, geranial, linalool and citronellol, is one of the most important terpenes known and considered to be a green reagent as it can be obtained from bio-renewable sources.

It can be isolated from naturally-occurring oils as a non-racemic mixture of its R and S enantiomers by steam distillation or solvent extraction. The latter is achieved by first forming the crystalline bisulphite aldehyde addition from oils containing a large percentage of the aldehyde, such as citronellal oil and oil of Eucalyptus maculate.[34]

Citronellal can also be produced using various synthetic routes, one of those being the formation from a rhodium complex as shown in Scheme 1.5.

A. $[RhCl(1,5\text{-}C_8H_{12})]_2 + 2(+) - BINAP \longrightarrow [Rh\ \{(+) - BINAP)\ (1,5\text{-}C_8H_{12})]^+ ClO_4^-$

$[RhCl(1,5\text{-}C_8H_{12})]_2 + 2(-) - BINAP \longrightarrow [Rh\ \{(-) - BINAP)\ (1,5\text{-}C_8H_{12})]^+ ClO_4^-$



(3*R*)-*N*,*N*-diethyl-3,7-dimethyloct-6-en-1-amine (R)-(+) Citronellal

Scheme 1.5: Synthesis of citronellal using a rhodium complex

The product citronellal produced is 99.4% chemically pure by GLC and has an optical purity of 95.2%.[35,36]

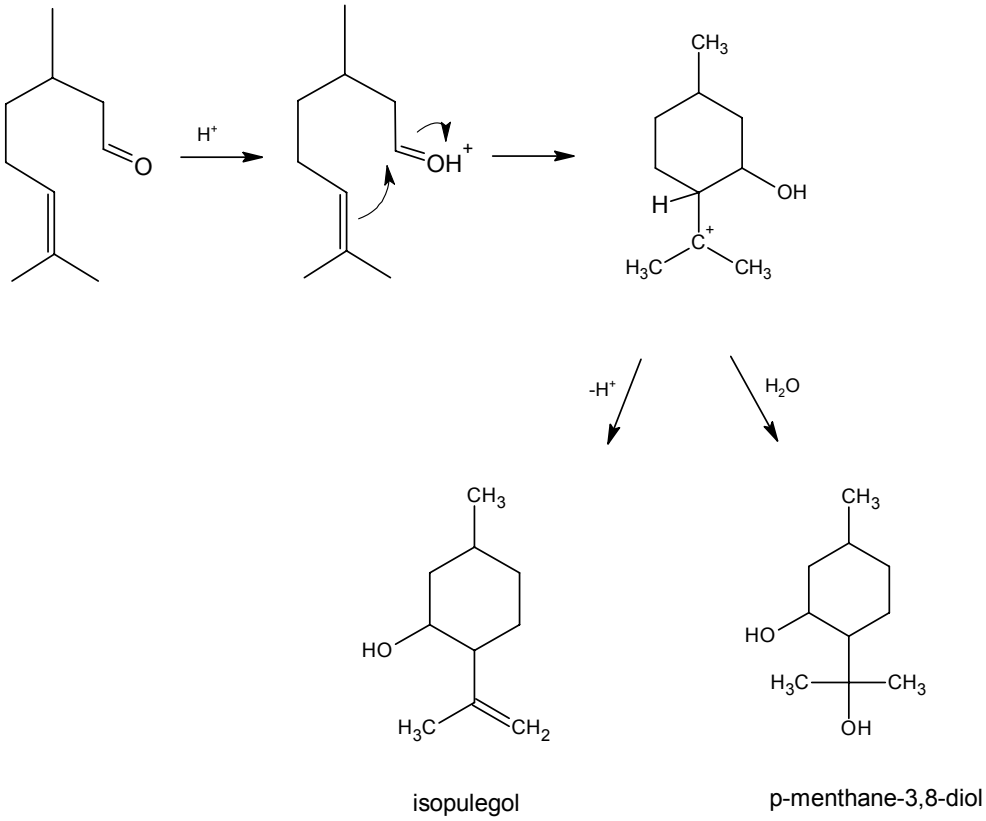
Citronellal can also be produced from pulegone ring opening using nucleophiles such as NaOH, $LiNMe_2$ and LAH via citronellol or citronellic acid.[37] Citronellal can also be synthesized by hydrogenation of citral[38] (Scheme 1.10).

1.10.7.2. Synthesis of p-menthane-3,8-diol

p-Menthane-3,8-diols may conveniently be formed through the direct acid-catalyzed cyclization of citronellal. This involves the intra-molecular addition of an aldehyde

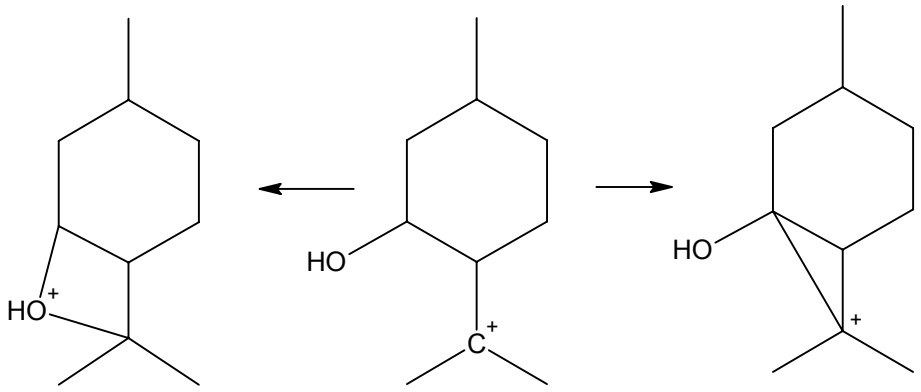
group to a double bond in the presence of an acid catalyst (although basic catalysts may also be used) according to the so-called Prins reaction.[39]

The reaction mechanism is believed to involve acid protonation of the carbonyl group, followed by the nucleophilic attack of the double bond on the resulting carbocation to form a protonated alcohol. The protonated alcohol can undergo loss of a proton to give the olefin (isopulegol), or addition of water to give the diol[40] (p-menthane-3,8-diol) as shown in Scheme 1.6.



Scheme 1.6: The synthesis of p-menthane-3,8-diol using citronellal as starting material

It has been proposed that the protonated intermediate is stabilized by neighbouring group interaction, with either the oxygen[41] or a carbon stabilizing the charge as shown in Scheme1.7.[41]



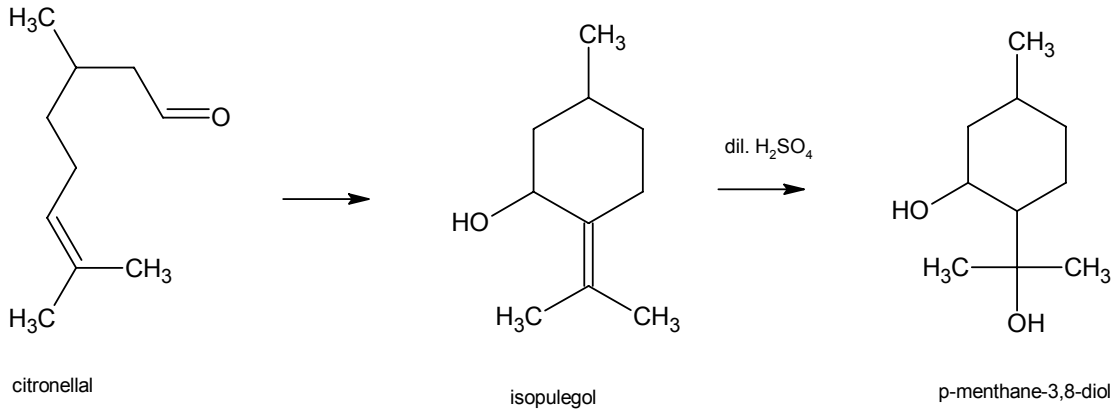
Scheme 1.7: Stabilization of the carbocation

In the case of the above example, the stability of the olefin increases with alkyl substitution as stated by the Markonikov rule.[42,40] The rule generally states that the more highly substituted carbocation would rather be formed as an intermediate than the less highly substituted carbocation. This means that an olefin such as citronellal carbocation that has two alkyl groups at its double bond carbon will easily allow the electrophillic attack by water, leading directly to the formation of p-menthane-3,8-diol as a product.

1.10.8. Synthesis of p-menthane-3,8-diol from isopulegol

Isopulegol is a monoterpenic alcohol which is widely employed in the fragrance and perfume industry for the production of fragrances with blossom compositions. It is also used as raw material for the production of menthol. Isopulegol is produced from citronellal by an ene type cyclization of (R)-citronellal, which occurs with 100% atom economy and results in four possible stereoisomers. The process involves heating citronellal between 130 and 200°C, or by irradiating citronellal with ultraviolet light. Thermal cyclization is accelerated by activated carbon, silica gel, diatomaceous earth doped with SiO_2, metal oxides, boric acid, bismuth triflate, nickel sulfate in a H_2 stream, or Cu-Cr and Cu-Cr-Mn catalysts, or in the presence of hetero polyacids such as those from the Keggin series.[43]

After the formation of Isopulegol, the double bond can be hydrated to form p-methane-3,8-diol by treatment with water and an acid catalyst, preferably sulphuric acid, but other acids such as nitric acid or perchloric acid can also be used.

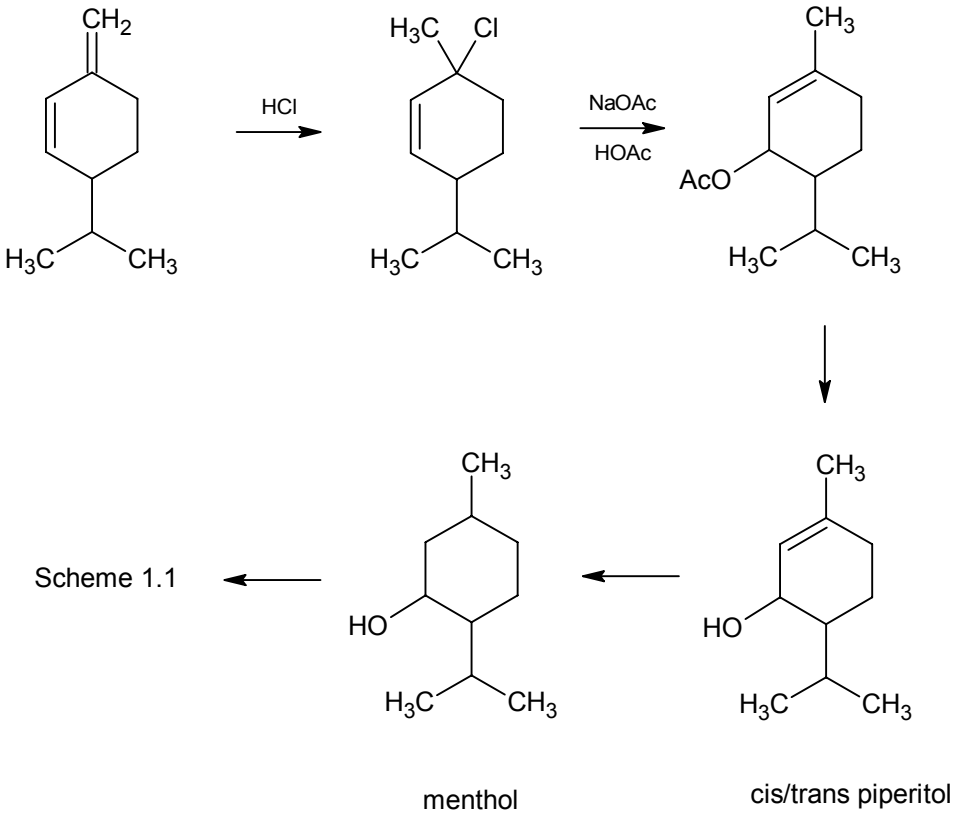


citronellal isopulegol p-menthane-3,8-diol

Scheme 1.8: The citronellal to isopulegol to p-methane-3,8-diol route.

1.10.9. Synthesis of p-menthane-3,8-diol from phellandrene

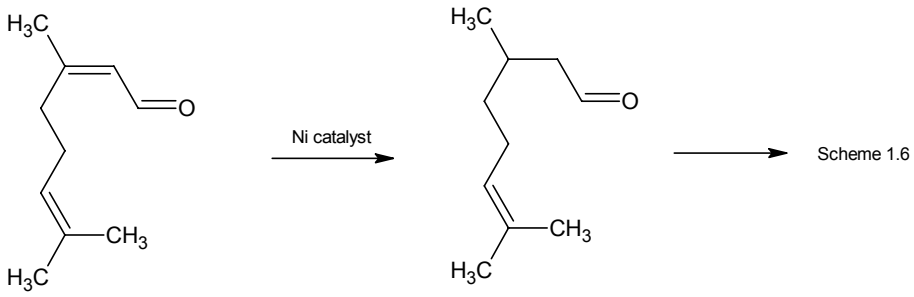
β-Phellandrene is the major constituent found, in high optical purity, in the turpinetine of the lodgepole pine (Pinus contorta). By adding hydrogen chloride to either β-phellandrene or α-phellandrene, phellandrene hydrochloride is formed (Scheme 1.9). Phellandrene hydrochloride can be converted to a mixture of optically active cis- and trans-piperityl acetates by allylic displacement of the chloride with sodium acetate in acetic acid. Hydrolysis of the piperityl acetate product produces piperitol, which can then be selectively hydrogenated to form menthol. Menthol, in turn, can be oxidized and reduced to form p-methane-3,8-diol (Scheme 1.1).[44,45]



Scheme 1.9: Synthesis of p-menthane-3,8-diol using phellandrene as starting material

1.10.10. Synthesis of p-menthane-3,8-diol from citral

Citral is an aroma compound used in perfumery for its citrus aroma. Citral can also be used to synthesize p-methane-3,8-diols via citronellal as an intermediate step. This can be achieved by hydrogenating citral using Ni-catalysts. These catalysts show very high selectivity towards the conjugated C-C double bond of citral, producing citronellal in high selectivities and conversions up to 80%.[46]



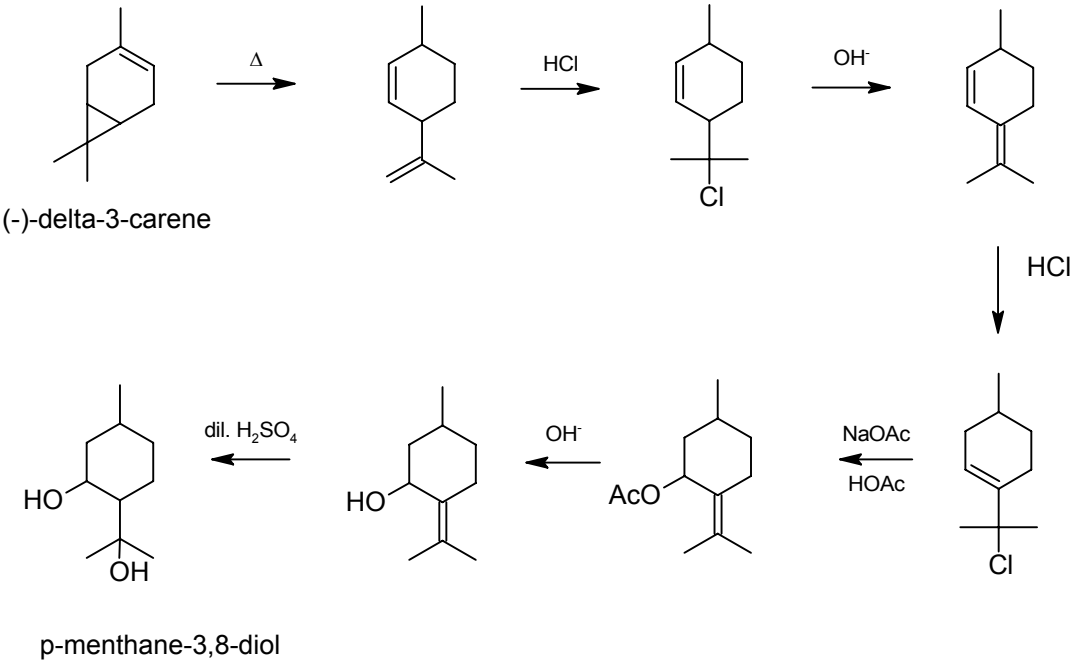
Scheme 1.10: Synthesis of citronellal from citral

After the reduction of the conjugated double bond, citronellal can be converted to p-menthane-3,8-diols through the direct acid-catalyzed cyclization of citronellal previously shown in Scheme 1.6.

1.10.11. Synthesis of p-menthane-3,8-diol from (-)-delta-3-carene

Delta-3-carene is a bicyclic monoterpene which occurs naturally as a constituent of turpentine. Its content in turpentine can be as high as 42% depending on the source of the turpentine. Delta-3-carene has a sweet and pungent odour. It is not soluble in water but miscible with fats and oils. It can be used as a possible starting material for the synthesis of p-menthane-3,8-diol.

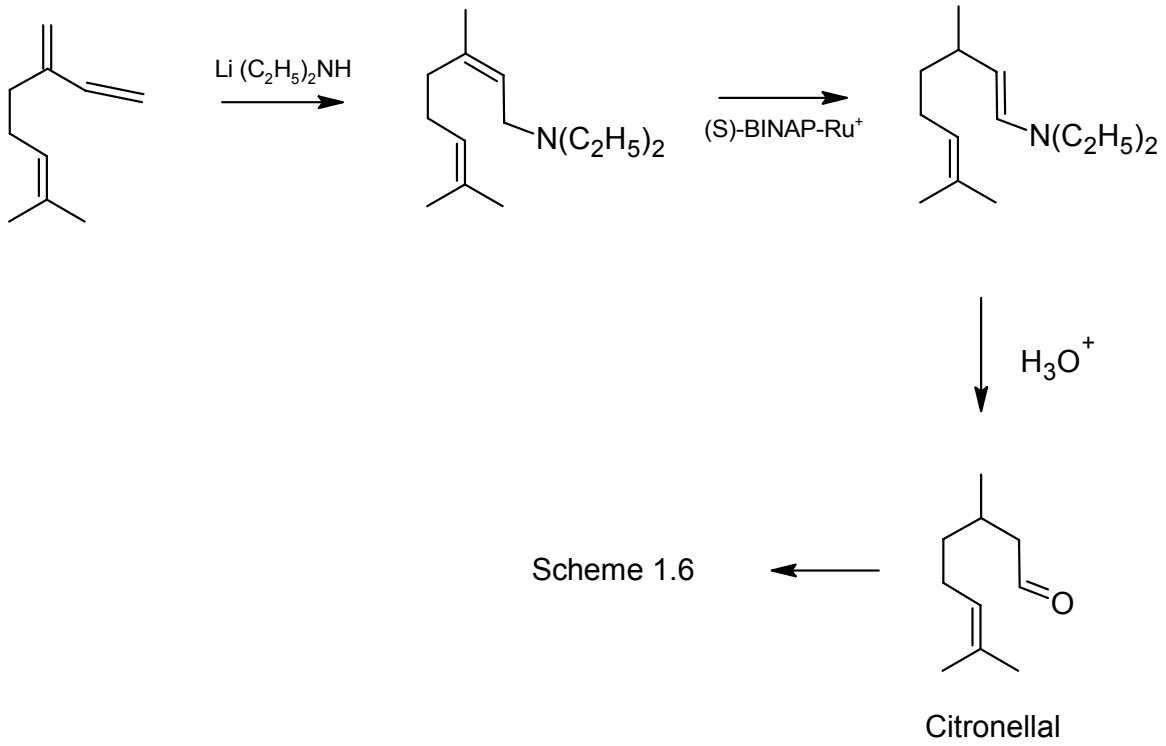
Through the synthesis of p-menthane-3,8-diol from delta-3-carene, pyrolysis of delta-3-carene results in the formation of 2,8-p-menthadiene. By using strong bases (e.g., potassium *t*-butoxide), or via hydrochlorination-dehydrochlorination, the 2,8-*p*-menthadiene can be isomerized to form 2,4(8)-p-menthadiene (Scheme 1.11). Once this is formed, further treatment of 2,4(8)-*p*-menthadiene with hydrogen chloride produces 8-chloro-3-p-menthene, which can be reacted with sodium acetate and acetic acid to give mixed (cis/trans) pulegol esters via allylic displacements. Hydrolysis of the pulegol esters results in the formation of cis/trans pulegol.[47] The acid-catalyzed hydration reaction of pulegol with dilute sulphuric acid results in the formation of p-menthane-3,8-diol as shown in Scheme 1.11:



Scheme 1.11: Synthesis of p-methane-3,8-diol using delta-3-carene as starting material

1.10.12. Synthesis of p-menthane-3,8-diol from myrcene

Myrcene occurs naturally in essential oils and can be used to synthesize p-methane-3,8-diol via citronellal as an intermediate.[47] A synthesis for the production of menthol from myrcene was first developed by Takasago Japan in the early 1980's (Scheme 1.12). During the synthesis, myrcene is converted to diethylgeranylamine by the lithium-catalyzed addition of diethylamine. The latter is then catalytically isomerized to the chiral 3R-citronellal enamine with 96-99% enantiomeric excess. Hydrolysis gives 3R-(+)-citronellal of higher chiral purity than citronellal from citronella oil. The remainder of the synthesis follows the synthesis of p-methane-3,8-diol discussed earlier (Scheme 1.6).



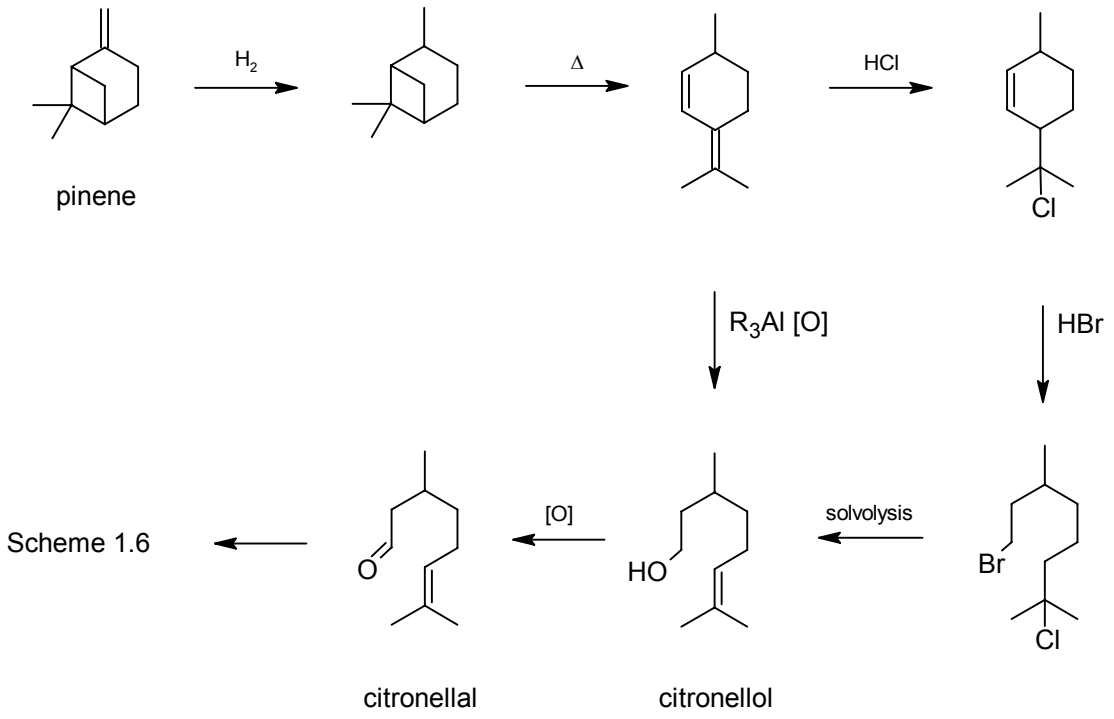
Scheme 1.12: Synthesis of p-menthane-3,8-diol using myrcene as starting material

1.10.13. Synthesis of p-menthane-3.8-diol from pinene

p-Menthane-3,8-diol can be produced from pinene in a manner similar to the synthesis of menthol from beta-pinene as was developed by Glidden-Durkee (SCM Corporation) in the early 1960's.[47] β-Pinene of very high optical purity occurs as a major constituent in both gum and sulphate turpentine produced in the eastern United States. These types of turpentine contain 60-65% α-pinene and 20-35% β-pinene from which the latter is commercially separated by fractional distillation for use as a raw material in resins and for perfume and flavour materials such as geraniol, linalool, citral, nopol, and a multitude of related aromatics.

The synthesis p-menthane-3,8-diol from pinene (Scheme 1.13) does not require separation of the isomers. Hydrogenation of pinene results in cis-pinane which can be pyrolysed to 2,6-dimethyl-2,7-octadiene. The latter can be converted to (+)-

citronellol by several routes.[48] One procedure involves protection of the 2,3-double bond by reaction with HCl to form 2-chloro-2,6-dimethyl-7-octene, followed by anti-Markownikoff addition of HBr.[49]

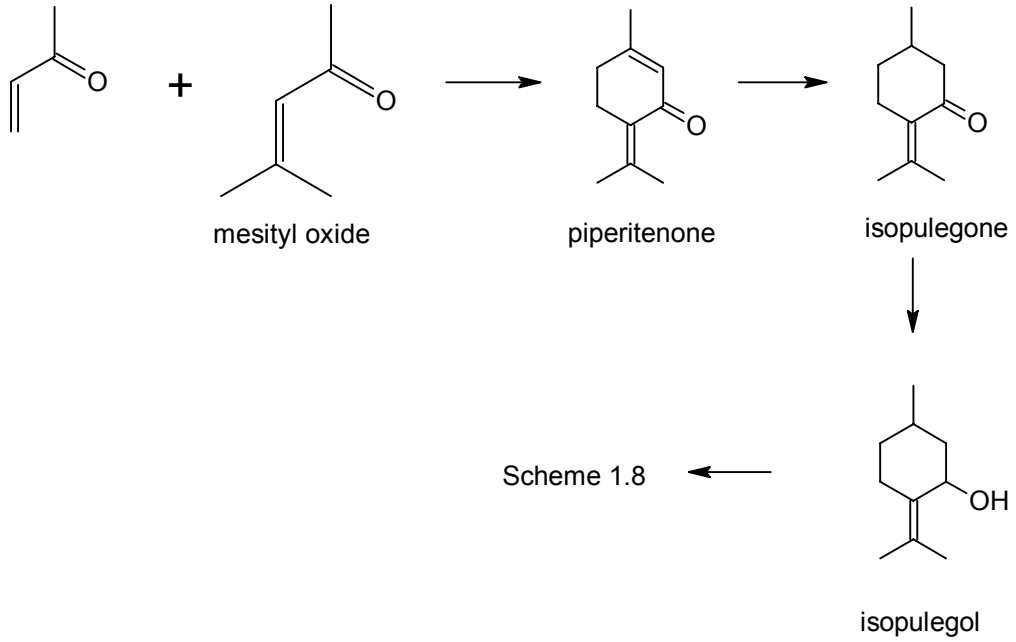


Scheme 1.13: Synthesis of p-methane-3,8-diol from pinene

Solvolysis of the intermediate bromo-chloro compound affords a mixture of α- and β-citronellol, either directly or more usually as the ester. Alternatively, direct treatment of 2,6-dimethyl-2,7-octadiene with organoaluminum compounds such as aluminum triisobutyl (or alkyl boranes)[50,51,52] and oxidation-hydrolysis affords citronellal in high yield. However, the treatment of 2,6-dimethyl-2,7-octadiene with organoaluminium compounds offers considerable advantages over the former, provided appropriate safety precautions are employed. Catalytic oxidation of (+)-citronellol gives (+)-citronellal in good yield.

1.10.14. Synthesis of p-menthane-3.8-diol from mesityl oxide

In early 2002, Takasago was issued a patent for the preparation of menthol from mesityl oxide via piperitenone.[53] While the Takasago processes utilizes chiral hydrogenation catalysts at several stages, this is not a requirement for the p-menthane-3,8-diol synthesis (Scheme 1.14), and the only key critical step is the conversion of piperitenone to pulegone, which can be achieved in about 90% yield. This process is however very unlikely to be used on a commercial basis as mesityl oxide is difficult to obtain.



Scheme 1.14: Synthesis of p-menthane-3,8-diol from mesityl oxide

1.11. Route selection

Of the potential methods discussed above, the synthesis involving the cyclization of citronellal appears to offer substantial advantages over the other routes, including:

1. The reaction only needs one catalyst, i.e., sulphuric acid in water and may be disposed of after neutralization as a dilute sodium sulphate solution in water.

2. The reaction can be performed at moderate temperatures which implies that equipment costs will be relatively low.

3. The synthesis produces only one intermediate and one significant by-product which will simplify product workup and purification.

4. Synthetic citronellal is commercially available from BASF at a reasonable cost (ca. $8 – 9/Kg) which should ensure stable raw material supply into the envisaged business.

In view of the above considerations, citronellal was chosen for the synthesis of p-menthane-3,8-diol. In view of the previous work done on the formulation of insect repellent products containing p-menthane-3,8-diol, preliminary specifications (initial development in the lab and market evaluations) were set for the production process, namely:

p-Menthane purity: 97.0% (Minimum)
Overall allowable amount of by-products (including unreacted starting material, reaction intermediate and by-products): 3.0% (Maximum).

These specifications were nonetheless only preliminary and after further negotiations with potential users of p-menthane-3,8-diol, the specifications were re-evaluated. A higher quality product would in a sense also be more advantageous as it would be more valuable and also minimize the amount of waste that would be produced, which

affects the cost of production. The revised specifications that were set for the full commercial process were:

p-Menthane purity: 99.0% (Minimum)
Overall allowable amount of by-products (including un-reacted starting material, reaction intermediate and by-products): 1.0% (Maximum).

1.12. New technologies for process development

Process development for fine chemical production usually involves the use of batch reactors, and this requires careful consideration of many different aspects when scaling up such processes. The development of micro-structured reactor technologies has paved the way for the consideration of continuous processing instead of batch processing when considering fine chemical production. Micro-structured devices for synthetic purposes were first introduced in the late 1980's and have since attracted great attention in the chemical engineering society as they offer exceptional technical advantages for a large number of synthetic applications.[54] These advantages often relate to their small size and these are discussed in the following sections.

1.12.1. Decrease of linear dimensions

The decrease in linear dimensions in micro-structured reactors decreases the respective gradients for a given physical property. This refers to properties particularly important to processing in chemical reactors, such as temperature, concentration, density, or pressure which are the driving forces for heat transfer, mass transport, or diffusional flux per unit volume or unit area.

1.12.2. Increase of surface-to-volume ratio

The narrow channels and thin fluid layers in micro-structured reactors allows for a drastic increase of surface-to-volume ratios. Specific surfaces of micro-channels range between 10000 - 50000m^2/m^3, whereas typical laboratory and production vessels usually do not exceed 1000m^2/m^3 and 100m^2/m^3, respectively. Apart from benefits of heat transfer, this increase in surface-to-volume ratio can also be exploited to increase the contact between reagents, or a reagent and a catalyst, e.g., in catalytic gas phase reactors coated with the active material on the inner walls.

1.12.3. Decrease of reactor volume

Due to the reduction of the linear dimensions in micro-structured reactors, the reactor volume of such reactors is significantly decreased compared to large-scale batch reactors, typically amounting to a few micro-litres. This significant difference becomes important when conducting very hazardous reactions or reactions in explosive regimes. The smaller hold-up increases process safety and in many instances improves selectivity of a process as reaction times can more easily be controlled as a function of flow rate(s).

1.13. Advantages of using micro-structured reactors for chemical synthesis

As mentioned earlier, micro-structured reactors have mostly been the interest of engineers and not chemists from the non-industrial research arena. This is mostly due to the fact that several years passed before the new technology was available to demonstrate its potential. Since then, many well known chemical syntheses, such as the Wittig, Knoevenagel, Aldol, Ugi and lots more, have successfully been carried out in micro-structured reactors with improved results when compared to their

conventional counterparts. These advantages extend over a wide area and will be discussed below.

1.13.1. Batch versus continuous processes

At present, a number of processes in the finechemical and pharmaceutical industry are carried out batch-wise, e.g. utilizing multi-batch reactors. In some cases, reaction times are set much longer than kinetically needed due to the slow mass and heat transfer in systems with low surface area-to-volume ratios.

Replacing this equipment by a continuous flow process in a microreactor can, due to fast transport in thin fluid layers, result in notably decreased contact times. In addition, conversion and selectivity may increase as has been demonstrated for several organometallic reactions.[55] Thus, space-time yields of micro-structured reactors can exceed that of batch processes.

1.13.2. Intensification of processing

Specific properties of micro-structured reactors such as their high heat transfer capacities, intensive mixing, and inherent safety (due to small volumes), allows operating under conditions previously not practical or safe. This allows for significant intensification of process conditions using micro-structured reactors which can result in significant increases in throughput rates.

1.13.3. Change of product properties

For polymer and multi-phase formation, where conformational, or compositional characteristics, or morphological properties are important, e.g., as for the generation of supramolecular structures such as liposomes, and microemulsions, these features

are very dependent on micro-mixing phenomena. Micro-structured reactors are specifically well suited for application in these fields as has been demonstrated through the uniform size and weight distribution of polymers, and size distribution of droplets in semi-solid pastes.[55]

1.13.4. Distributed production

At present, chemical production is generally carried out in large production plants due to economy of scale considerations. In addition, the advent of small, self-contained production platforms, based on the principles of micro-structuring, has revived the concept of "Just-in-Time" (JIT) manufacturing, especially in the pharmaceutical industry where keeping stock of expensive active ingredients can put a substantial strain on cash flows. Realising the objective of distributed production, JIT production at the site of use is a substantial driving force in several R&D initiatives involving the development of micro-structured, or related continuous-flow production technologies.

1.13.5. Scale up

Conventionally, chemical process development would take place via a sequence of intermediate stages where the reaction volume is successively increased from laboratory scale to production scale of several kilotons per annum. This "scale-up" process is not only time consuming and expensive, but problems arising from scale-effects often require redesign and rework. In contrast to conventional "scale-up", there exists the opportunity to convert laboratory production processes to full production-scale processes through a system involving a multitude of parallel laboratory-scale processes in a "numbering-up" manner by using micro-flow devices to meet large chemical demands.[55]

1.14. Reactions generally performed in the fine chemicals production

In evaluating the potential of the opportunity that micro-structuring brings to chemical processing, one can perhaps ask what type of reaction would benefit from the advantages of micro-structuring (mentioned above) to some or other degree. One way would be to consider the different types of reactions performed in the fine chemicals industry, by classifying the reactions according to their kinetic properties, as discussed now.

1.14.1. Type A

Reactions where the half-life of the reaction is less than one second. These reactions are very fast. The bulk of the reaction occurs within the mixing zone. In general, the objective for such reactions should be to balance the rate of mixing to the rate of the reaction so as to minimize local concentration gradients. Typical examples of such reactions would be highly reactive species such as some halides, amines, acid chlorides and organometallic reactions, such as Grignard-type chemistry, to name but a few.

1.14.2. Type B

Reactions where the half-life of the reaction is between one second and ten minutes. While such reactions are still very fast, reactions are generally no longer critically dependent on the rate of mixing. Scale-up for such reactions can be significantly simplified by maintaining volume to surface area ratios so as to ensure consistent concentration and temperature gradients. In addition, the potential to intensify such reactions may result in significant productivity advantages.

1.14.3. Type C

Reactions where the half-life of the reaction is greater than 10 minutes. These reactions are slow and suit typical batch processing, except in cases which either involve hazardous reagents, or potentially hazardous thermal events (reagent, intermediate, product decomposition, etc.).

Within the above reaction types, one can possibly define further sub-classes based on the nature of the reaction mechanism. These are referred to below:

1.14.4. Class 1

Reactions that involve single reactions that produce a single product or a product with one or more by-products, in a fixed ratio as determined by the reaction mechanism from one or more feeds.

1.14.5. Class 2

These reaction systems comprise additional reactions in parallel to the main reaction producing further by-products. Reactions in parallel are defined as the reaction of the feed or feeds, with themselves or other materials (e.g. solvent) in the reactor, excluding reaction products.

1.14.6. Class 3

These reactions system comprise additional reactions in series to the main reaction to produce further by-products. Series reactions involve the further reaction of the reaction product of the primary reaction.

1.14.7. Class 4

These reaction systems comprise additional reactions of both the last two types, parallel and series.

1.14.8. Class 5

These are polymerization reactions.

What is striking is that 70% of the reactions mentioned above are currently performed in a semi-batch manner in the fine chemical and pharmaceutical industry.[56] These reactions are mainly controlled by the dosage of one reagent, with the consequence that the reaction vessel is oversized in terms of its active volume. Hence the space-time yields for such vessels are relatively low and a continuously operated reactor would in principle be better suited to such reaction kinetics.

What is also noteworthy is that 60% of the reactions mentioned contain some form of solid, whether as reactant, catalyst or product. This, however, is problematic for micro-structured reactors that are currently available as this leads to fouling of the internal structures of the micro-channels and also highlights one of the disadvantages of these miniature systems. To date, the use of micro-structured reactors is limited to homogeneous reactions and to some extent, to gas-liquid and liquid-liquid reactions. Nonetheless, the advantages of micro-structured reactors outweigh the disadvantages.

1.15. SMME's (small, medium, and micro enterprises)

It has already been mentioned that one of the South African government's objectives in order to obtain a sustainable economical growth is to target the growth of the chemicals sector. One way of meeting this particular objective is to promote entrepreneurship and growing the small to medium enterprise sector. This strategy would progressively increase the development in critical areas such as job creation, equity and access to various markets as it has been found across the world that SMME's play a critical role in absorbing labour, penetrating new markets and generally expanding economies in creative and innovative ways.[57]

In order to facilitate these initiatives, the South African government has identified numerous constraints which hinder the development of such. These constraints most commonly relate to the legal and regulatory environment, access to markets, access to finance and affordable business premises, the tax burden, and access to quality business infrastructure in poor areas. In the chemical industry, the high cost of equipment, the mere size of conventional plants, and also the specialized skills necessary to run such businesses have made it particularly difficult for the ordinary scientist to penetrate this area.

Micro-structured flow technology, or down-scaled production facilities that are still competitive with mega-plants provide the potential for the development and diversification of the fine chemical sub-sector in South Africa. This potential essentially relates to:

- Low initial capital investments and the potential to grow through a process of "numbering-up". Their small sizes also eliminate the burden of requiring large premises usually associated with chemical processing.
- The ability to produce economically for the available market. Generally, production volumes are related to reactor size. Below a certain production

rate, production costs rise sharply and reduce the economic viability of such processes.

1.16. Objective of this study

This study is concerned with the synthesis of p-menthane-3,8-diol via the acid-catalyzed cyclization of citronellal in a dilute aqueous sulphuric acid medium. The project is based on the hypothesis that the synthesis can be carried more effectively on a continuous basis in a continuous flow reactor than is possible in traditional batch reactors. (“Effective” in the context of this project implies both a higher reactor productivity, and higher efficiency as measured by overall yield and selectivity.)

The research strategy will consider a detailed comparison of batch synthesis and continuous-flow synthesis in order to determine the scalability of the two approaches. In addition, downstream processing of crude product will also be studied so as to meet specific product quality specifications.

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Chapter 2

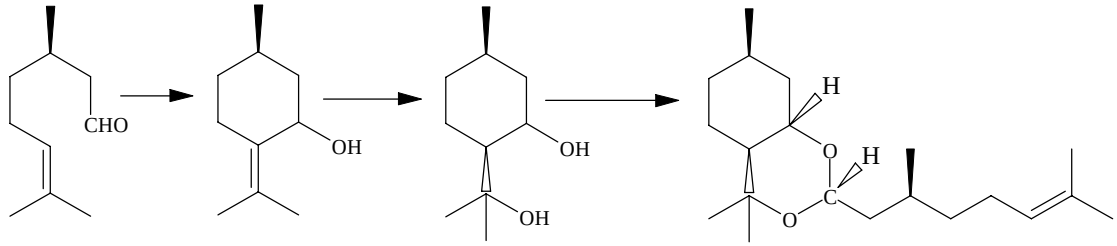
Synthesis of p-menthane-3,8-diol: batch reactor studies

Abstract

The synthesis of p-menthane-3,8-diol (PMD) was studied using batch reactor techniques with the view to obtain a clear understanding of the reaction kinetics and the reaction mechanism at work. The results obtained show that the formation of PMD from citronellal occurs via an intra-molecular Prins reaction that results in the formation of both the desired PMD product, as well as the partially hydrated isopulegol. Clear evidence was obtained for the existence of an equilibrium between PMD and isopulegol; both the hydration reaction (from isopulegol to PMD) and the reverse dehydration reaction were catalyzed by the acid catalyst. The formation of the by-product, PMD-acetal, is believed to result from reaction between an intermediate 5-methyl-2-isopropylcyclohexanol intermediate and the citronellal starting material, not from the reaction between PMD and citronellal as previously reported. Kinetic studies confirm the existence of a complicated kinetic model for the formation of PMD from citronellal. At citronellal conversions up to about 70%, the reaction displays typical pseudo first order kinetics, but at higher citronellal conversions the kinetic model becomes complicated as the isopulegol/PMD equilibrium and the PMD-acetal formation reaction, which appears to be second order with respect to the PMD concentration, become important. This implies that operation of the synthesis reaction under conditions of high temperature will favour the formation of the desired di-hydrated PMD, and when citronellal conversion is restricted, keeps the degree of PMD-acetal formation to a minimum. Scale-up studies of the batch process to 30L and 50L scales showed that it would be extremely difficult to limit the level of PMD-acetal formation below the 1% desired level, even if citronellal conversions are restricted to about 50%.

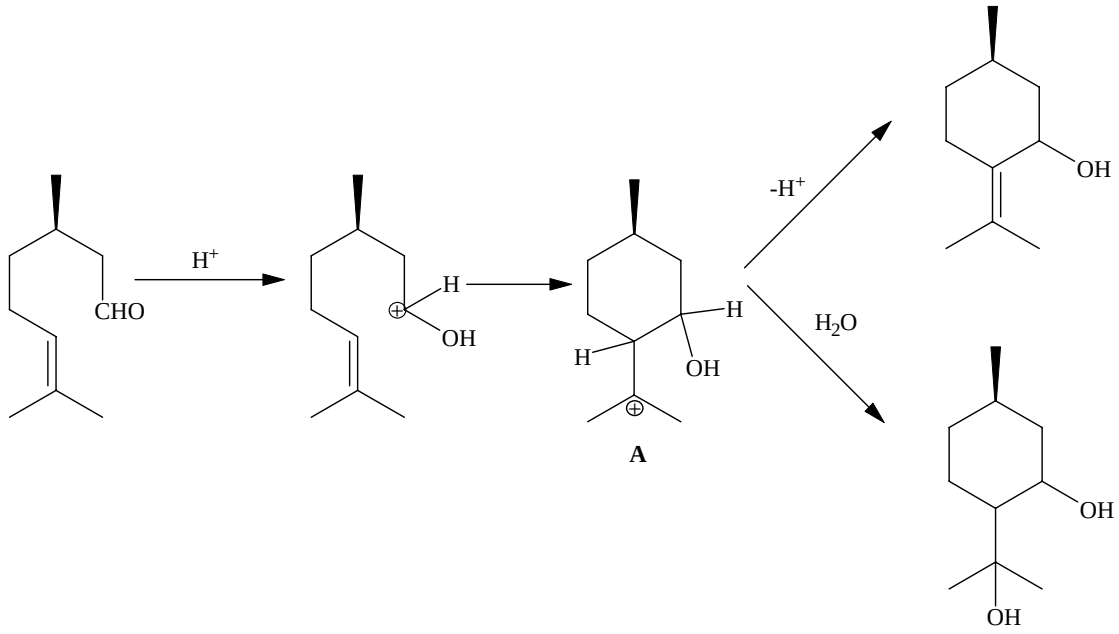
2.1. Introduction

A significant amount of information already exists with regards to the synthesis of PMD from citronellal. It was, for example, reported[1,2] that the general reaction sequence for the acid-catalyzed cyclization of citronellal to PMD proceeds via isopulegol as intermediate when the reaction is carried out in the presence of dilute (0.25%) sulphuric acid as catalyst (Scheme 2.1).

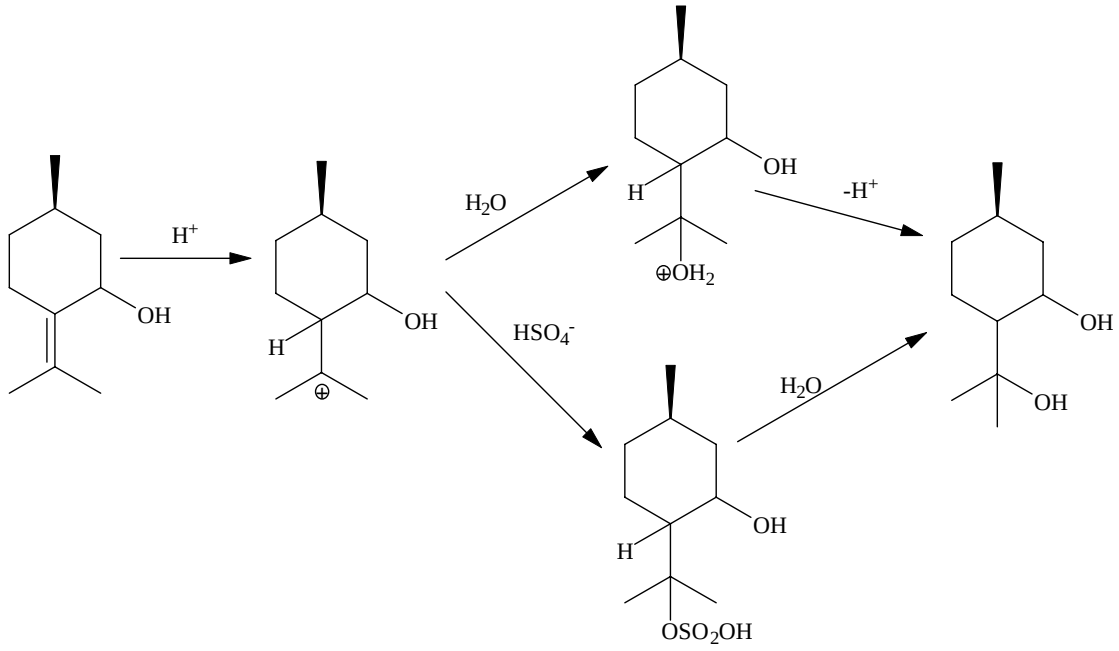


Scheme 2.1: General scheme for the synthesis of PMD

It was also suggested that the reaction for the formation of PMD could in fact follow two different routes (Schemes 2.2 and 2.3). One allows the formation of an intermediate, isopulegol, followed by hydrolysis to form PMD (Scheme 2.3). The other route follows the formation of PMD straight form citronellal as illustrated in Scheme 2.2. These proposals are similar to the reported mechanistic routes for the intermolecular Prins reaction between aldehydes and alkenes.[3] At higher temperatures (above 85°C), the latter route is generally claimed to be favoured.



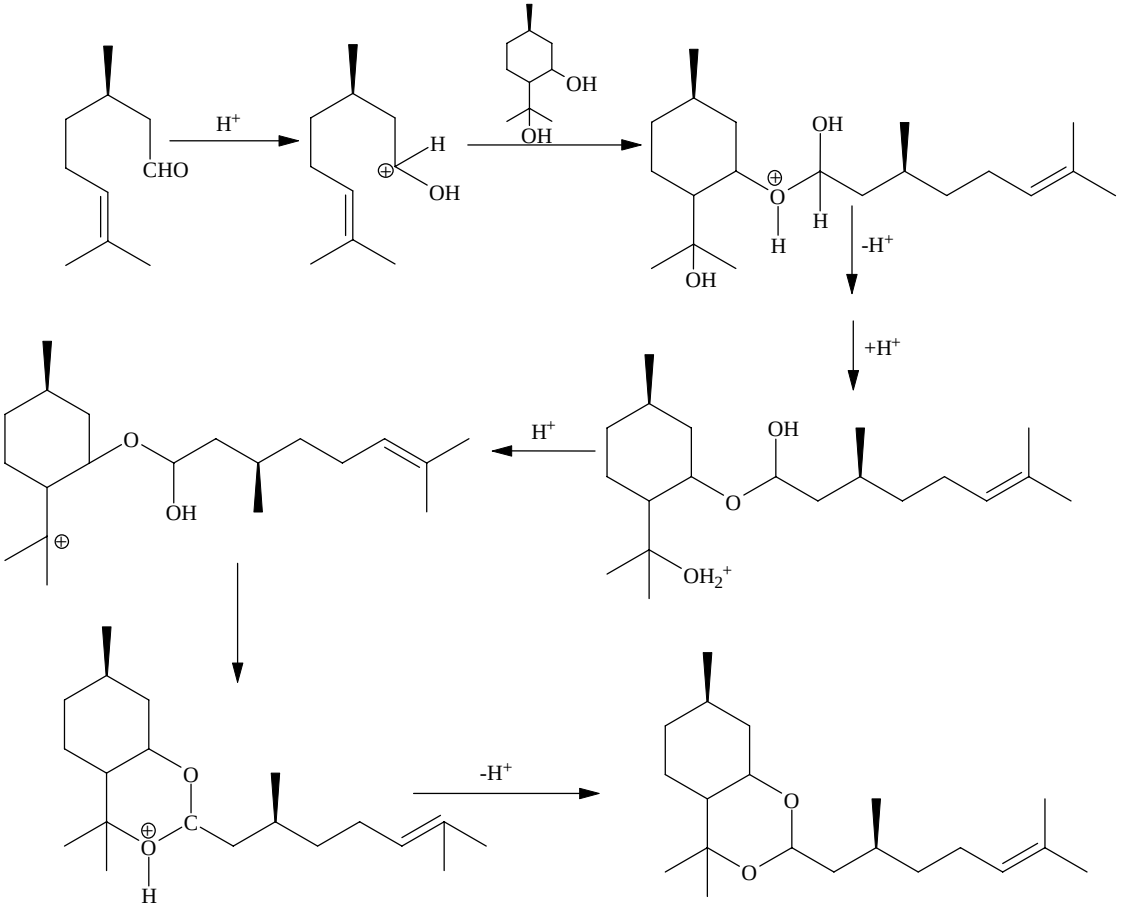
Scheme 2.2: The formation of isopulegol and PMD from citronellal



Scheme 2.3: The hydration step of isopulegol to form PMD as product

The formation of a by-product (PMD-acetal) was also observed,[1,2] and the route as shown in Scheme 2.4 was proposed to explain the formation of these PMD-acetals. According to this proposal, the formation of the PMD-acetal occurs as a result of the

reaction between the starting material, in this case citronellal, with PMD formed during the reaction, in a competitive consecutive reaction.



Scheme 2.4: Reaction mechanism for the formation of PMD-acetal

In order to fully evaluate the potential scale-up of the acid-catalysed cyclization of citronellal using batch reactor techniques, it was important to confirm (or otherwise) the previously reported mechanistic interpretations and to derive further information regarding the rates of formation of product and by-products. This part of the investigation reports on the findings of these investigations, as well as the results of attempts to scale-up the batch synthesis to 30L and 50L scales. These scale-up experiments were also carried out so as to synthesize enough material required for market evaluations.

2.2. Experimental

2.2.1. Materials

All the materials that were used for the synthesis of p-menthane-3,8-diol, the sources of procurement and the respective grades, are listed in Table 2.1, and were used as received unless otherwise specified. Solvents used for GLC analysis of reaction mixtures and isolated product are listed in Table 2.2.

Table 2.1: Reagents for synthesis

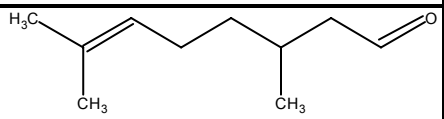
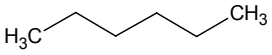
Name	Structure	MM g/mol	Supplier	Grade Purity
Citronellal		154.14	Merck	AR
Sulphuric acid	H_2SO_4	98.08	Merck	95-98%
Sodium bicarbonate	$NaHCO_3$	84.01	Saarchem	AR

Table 2.2: Solvents used for analysis

Name	Structure	MM g/mol	Supplier	Grade Purity
n-Hexane		86.1766	Merck	AR
Heptane	isomers	100.21	Merck	AR

2.2.2. Equipment setup

2.2.2.1. Lab-scale reactor setup

Lab-scale batch studies were carried out in a double-walled glass reactor. The reactor was fitted with an overhead stirrer (capable of stirring rates up to 2000rpm), a condenser, and thermometer to measure reaction temperatures. The jacket of the glass reactor was connected to a heater circulator bath filled with heat transfer oil to allow for reactions to be performed at elevated temperatures. The batch reactor setup is shown in Figure 2.1.

Figure 2.1: Double-walled glass reactor, equipped with overhead stirrer and connected to heater circulator bath

2.2.2.2. Pilot plant setup

Scale-up studies of the batch process were carried out using both a 30L and 50L Büchi ChemReactor system (Büchi GlasUster). These reactor systems form part of the Kilo-Laboratory Facility of InnoVenton, NMMU Institute of Chemical Technology. Both reactor systems are equipped with an agitator capable of multiple stirring rates, condenser, delivery and receiving vessels, and are connected to the kilo-laboratory's utilities system (including compressed air, vacuum system, thermal oil system, and chilled water). Temperature and pressure probes are connected to the reactor systems and are monitored via the kilo-lab's PLC system. Figure 2.2 shows a picture of the 30L Büchi Chemreactor system, while Figure 2.3 illustrates link-up of the reactor system with the utility and control system.

Figure 2.2: 30L Büchi Chemreactor system

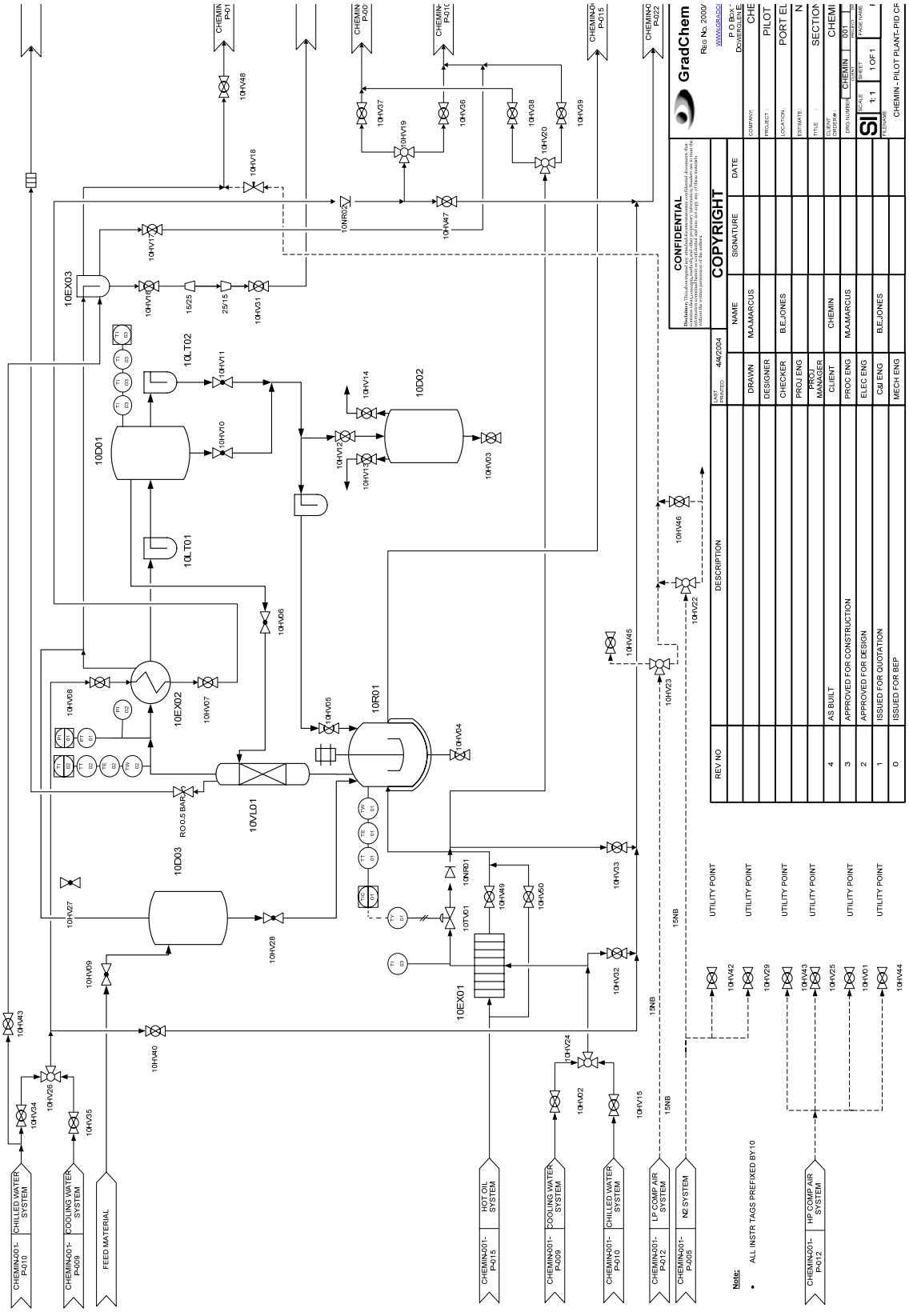


Figure 2.3: Schematic diagram of Büchi Chemreactor system layout

2.2.3. Synthetic Procedures

2.2.3.1. Lab-scale synthesis

Pure citronellal was reacted with aqueous sulphuric acid (0.3% v/v) in a ratio of 1 part organic to 4 part aqueous phase. The aqueous phase was added to a 0.5L double-walled glass reactor which was connected to a heater/circulator and allowed to equilibrate to the reaction temperature which was set to 85°C (Figure 2.1). When the aqueous phase reached the desired temperature, preheated citronellal (85°C) was added to the reactor as quickly as possible and the reaction time started.

The reaction mixture was stirred using an overhead stirrer, at 2000rpm for 7 minutes after which the stirrer was stopped, the two phases allowed to separate, and the aqueous phase drained off. A 2.5% sodium bicarbonate solution was then added to the organic phase with stirring to neutralize residual acid catalyst. Thereafter the organic phase was washed three times with hot (80°C) de-ionized water, each time discarding the aqueous layer and retaining the organic layer. The organic layer was then dried and analyzed by gas chromatography.

2.2.3.2. Kilo-lab synthesis (50L reactor)

During the synthesis of PMD on the pilot plant, 36.67kg of water was loaded into the 50L Büchi Chemreactor using a diaphragm pump. Thereafter 9.8kg of citronellal was added to the reactor by means of vacuum transfer. The agitator was set to the appropriate speed and thermal oil from the hot oil system, controlled via the PLC, system was allowed to flow through the jacket of the reactor in order to heat the reactor contents to the desired temperature of 85 ^{o}C.

Following equilibration to the desired temperature (indicated by the PLC system), 0.120kg of H_2SO_4, diluted with 0.88kg of water (ambient), was transferred to the reaction mixture in the 50L reactor by means of vacuum transfer and the reaction time started. The reaction was allowed to continue for a predetermined time.

Once the desired reaction time was reached, 0.33kg of sodium bicarbonate, dissolved in 2.92kg of water, was fed into the reactor over a period of 30s in order to stop the acid-catalyzed reaction. The agitator was then switched off and the organic and aqueous layers allowed to separate (5 min). Once the layers were separated, the aqueous layer was drained off and weighed. After the aqueous layer was drained off, 15.93kg of water was added to the organic phase using a diaphragm pump and the agitator switched on again. The mixture was allowed to stir for another 5min after which the agitation was stopped and the phases allowed to separate for about 15min.

Once separated, the aqueous phase was drained off and the organic phase retained in order to strip off the starting material by means of vacuum evaporation. The reactor temperature was set to 110°C and the pressure slowly reduced until a pressure reading of 1kPa was observed. The evaporation was allowed to continue until no more distillate was observed coming over. The reactor bottoms (crude PMD) and distillate (mixture of water and organics) were put into appropriate containers and kept for analysis.

2.2.4. Analytical procedures

2.2.4.1. Gas chromatography

Samples of the organic phases of reaction/product mixtures were diluted with heptane in the ratio one part sample and ten parts solvent before analysis on a Thermo-Finnigan Focus Gas Chromatograph (Model no: AI 3000). The chromatograph was equipped with a flame ionization detector, and a Econocap-5 column (film thickness 0.25µm; internal diameter 0.25mm; length 30m). Delta Chromatography software (Version 5) was used for recording and integrating of the chromatograms. Nitrogen was used as carrier gas and the carrier gas flow rate was kept constant at 1mL/min for all the analyses. The column temperature program used for the analysis of citronellal, PMD, and PMD-acetals is summarized in Table 2.3.

Table 2.3: Conditions for the analysis of citronellal, PMD and PMD-acetals

Carrier gas	Nitrogen
Column gas flow	1ml/min
Split ratio	40:20
Injection volume	1µL
Injection temperature	270°C
Detector temperature	280°C
Column initial temperature	70°C
Column temperature program	70°C for 5min, ramp to 270°C (10°C/min), isothermal for 5min.
Run time	30 minutes

Figure 2.4 illustrates a typical chromatogram for the analyses of reaction mixtures. Citronellal, Isopulegol, PMD, and PMD-acetals are indicated on the chromatogram. It should be noted that both PMD and the PMD-acetals are actually mixtures of stereo-isomers as can be seen from the chromatogram.

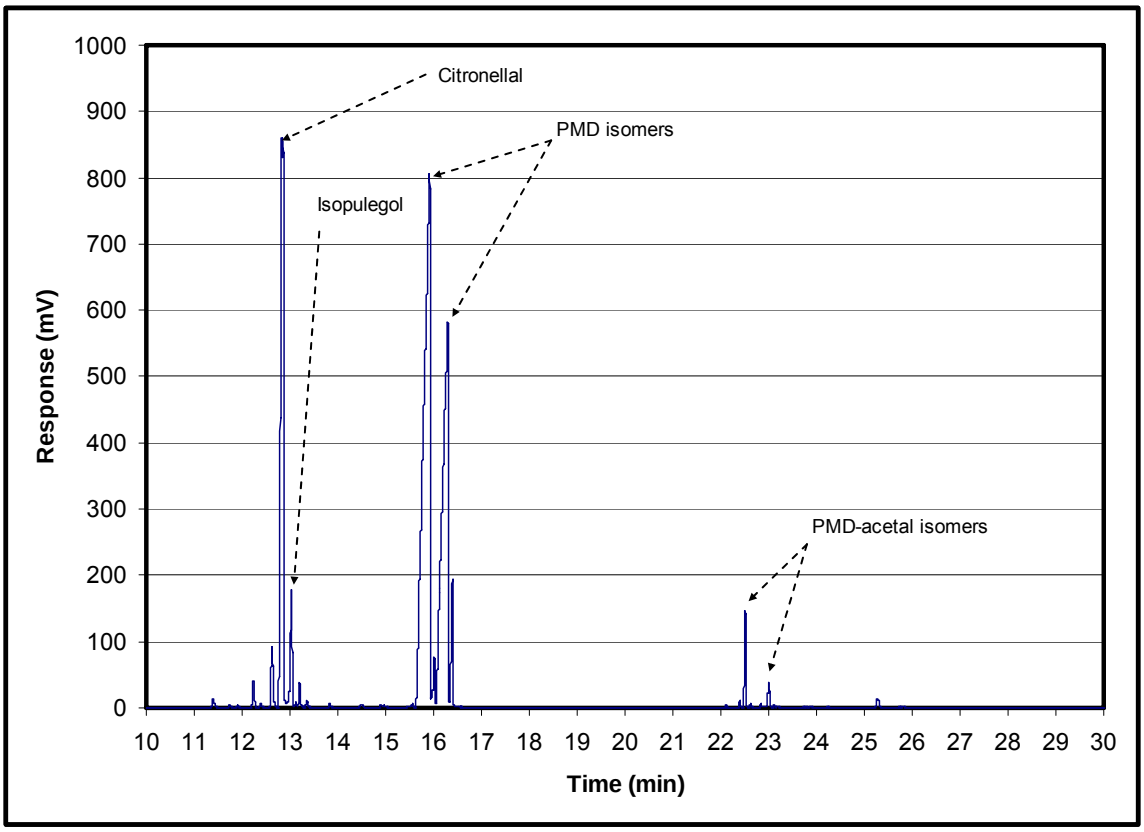


Figure 2.4: Typical GC chromatogram for reaction and product mixtures

2.2.4.1.1. Calculation of GC response factors and corrected peak areas

GC response factors and corrected peak areas for the individual components in reaction or product mixtures were calculated according to a previously published procedure.[4] Maximum response in a flame ionization detector is expected for organic compounds containing only carbon and hydrogen bonds. The presence of hetero-atoms such as oxygen will reduce the response in the detector, thereby lowering the GC response as measured by the area underneath the component peak. The peak area is therefore a measure of both the amount of carbon eluted within a peak, and also of the intensity of carbon atom ionisation within the particular component. Therefore the FID signal needs to be corrected for the carbon atoms bonded to atoms other than hydrogen. The average response factor (f_i) for a particular species

considers the different response in the FID of a carbon atom in the molecule that is bound to other atoms than hydrogen.

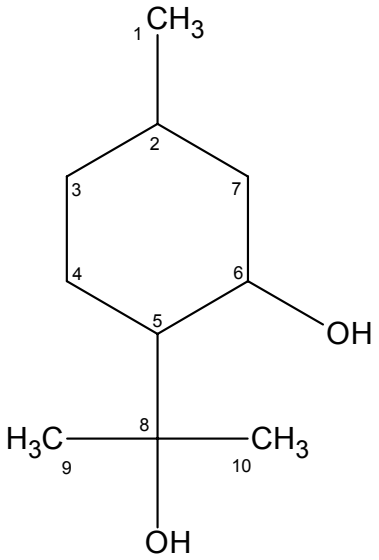
In order to calculate the various response factors, the molecular structures of the various compounds are used to determine the amount of carbon atoms (C_n) in each molecule. Each carbon atom was assigned a value = 1.

The ECN (effective carbon number) value was then determined by subtracting the average reduction in signal which each atom (other than hydrogen) bonded to carbon would produce. The number of carbon atoms would then be divided by the ECN value to determine the average response factor of a particular compound.

$$\frac{C_n}{ECN} = fi$$

For example, the average response factor for p-menthane-3,8-diol can be calculated as follows:

Molecular structure:



Number of carbon atoms = 10

Number of functionalities = 2 x –OH

Average reduction for alcohols = 0.64

Therefore: $$f_i = \frac{10}{(10 - 2 \times 0.64)} = 1.147 \qquad [2.1]$$

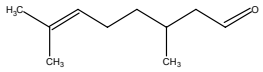
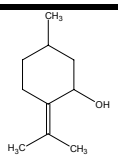
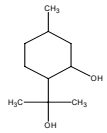
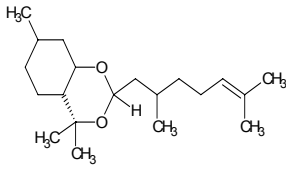
Table 2.4 summarizes the average reductions for atoms bonded to carbon and the respective error in prediction for compounds with multiple functionalities.

Table 2.4: Average signal reductions of hetero-atoms bonded to carbon

Class	ECN reduction	% Error in prediction
Nitrogen heterocycles	-0.62	1.7
Ketones	-0.80	1.6
Amines (primary)	-0.58	1.8
Alcohols and phenols	-0.64	2
Ethers and furans	-0.78	1.5
Esters	-1.27	0.8

Table 2.5 lists the number of carbon atoms, the ECN values and the corrected GC response factors for the starting material, product and by-products of the PMD synthesis reaction.

Table 2.5: Corrected GC response factors

Compound	Molecular structure	Carbon number (C_n)	Reduction	ECN	Corrected response factor
Citronellal		10	1 x 0.80	9.20	1.087
Isopulegol		10	1 x 0.64	9.36	1.068
p-menthane-3,8-diol		10	2 x 0.64	8.72	1.147
p-menthane-3,8-diol-acetal		20	2 x 0.78	18.44	1.085

The corrected peak areas (PAC_i) were calculated by multiplying the raw integrated peak areas (PA_i) obtained from the GC chromatogram with the corrected response factors listed in Table 2.5. For example, the corrected peak area for p-methane-3,8-diol (PAC_{PMD}) was calculated from the peak area (PA_{PMD}) as shown in Equation [2.2]

$$PAC_{PMD} = PA_{PMD} \times f_i \qquad [2.2]$$

2.2.4.1.2. Calculation of selectivity and molar percentages

To study the effect of different reaction variables during PMD syntheses, conversions, molar percentages and selectivity needed to be calculated. For the purpose of these

calculations, only major peaks such as citronellal, isopulegol, PMD, and PMD-acetals were considered. Solvent peaks, as well as minor unknown peaks were not considered. These calculations are based on the assumption that all of the substrate that entered the reactor came out in the form of intermediate, product or by-product, and starting material that was detected by the FID.

The relative percentage yields were calculated by dividing the respective corrected peak area of the component of interest by the sum of all the corrected peak areas (x100) in the chromatogram. For instance:

$$\%PMD = \frac{PAC_{PMD}}{\sum PAC_{ij}} \times 100 \qquad [2.3]$$

The percentage conversion for the substrate was calculated by dividing the sum of the corrected peak areas for all the reaction products by the sum of the corrected peak areas for the starting material and all reaction products.

$$\%\ Conversion = \frac{\sum PAC_{\mathrm{Pr}\,oducts}}{\sum PAC_{(Substrate\ +\ \mathrm{Pr}\,oducts)}} \times 100 \qquad [2.4]$$

The percentage selectivity for the individual reaction products were calculated by dividing the respective corrected peak area by the sum of the corrected peak areas of all the reaction products. The PMD selectivity is used as an example.

$$\%\ PMD\ Selectivity = \frac{PAC_{PMD}}{\sum PAC_{\mathrm{Pr}\,oducts}} \times 100 \qquad [2.5]$$

2.2.4.2. GC-MS analysis

G.C-Mass spectrometry was performed on a 5890 series II plus gas chromatograph coupled to a HP 5972 series mass selective detector. The GC was equipped with a HP-5 MS capillary column (30mm x 0.25mm i.d). Data were acquired from the detector by means of a Hewlett Packard personal computer equipped with HP 61034 C software. The GC was fitted with an RTX 35ms column (length 30m x 0.25mm ID x 0.25cm thickness) and the column oven temperature was programmed as follows:

Table 2.6: Conditions used for the GC-MS analysis

Initial column temperature (°C)	70
Initial column hold time (min)	5
Heating rate (°C/min)	10
Final column temperature (°C)	250
Final column hold time (min)	5
Injector temperature (°C)	250
Split flow	60 mL/min
Carrier gas	Helium at constant flow
MS-mass range	30 – 350 amu

2.2.4.3. Analysis of sulphuric acid

The sulphuric acid content of the initial aqueous phase solutions was determined by titrating against a standardized NaOH solution. Potassium hydrogen phthalate (KHP) was used to standardize the sodium hydroxide. To determine the sulphuric acid content, a 25mL aliquot of the aqueous phase was titrated against a standard 0.1016M NaOH solution to a phenolphthalein indicator end point.

2.3. Results and discussion

2.3.1. Mass transfer

The synthesis of p-menthane-3,8-diol by the acid cyclization of citronellal is carried out as a two-phase, aqueous/organic reaction. Mass transfer between the two phases will therefore play a critical role in determining the reaction kinetics and the eventual outcome of the reaction. Such mass transfer phenomena are particularly relevant in the case of reaction systems that contain by-product formation reactions that occur in series to the product formation reaction, as a low mass transfer rate will significantly increase reactor residence times, and hence the probability that the series by-product reaction can take place.

To show the effect of mass transfer which, in a stirred batch reactor is influenced by the degree of mixing, hence the stirring speed, a number of experiments were conducted to determine the optimum stirring speed where the reaction would not be mass transfer limited (Fig. 2.5). These reactions were carried out in a 500cm^3 batch reactor fitted with overhead stirrer and turbine impeller. Reactions were performed as described in Section 2.2.3.1 and by varying the stirrer speed between 750 and 1750rpm. At the end of the pre-determined reaction period, the citronellal conversion was determined by GC analysis.

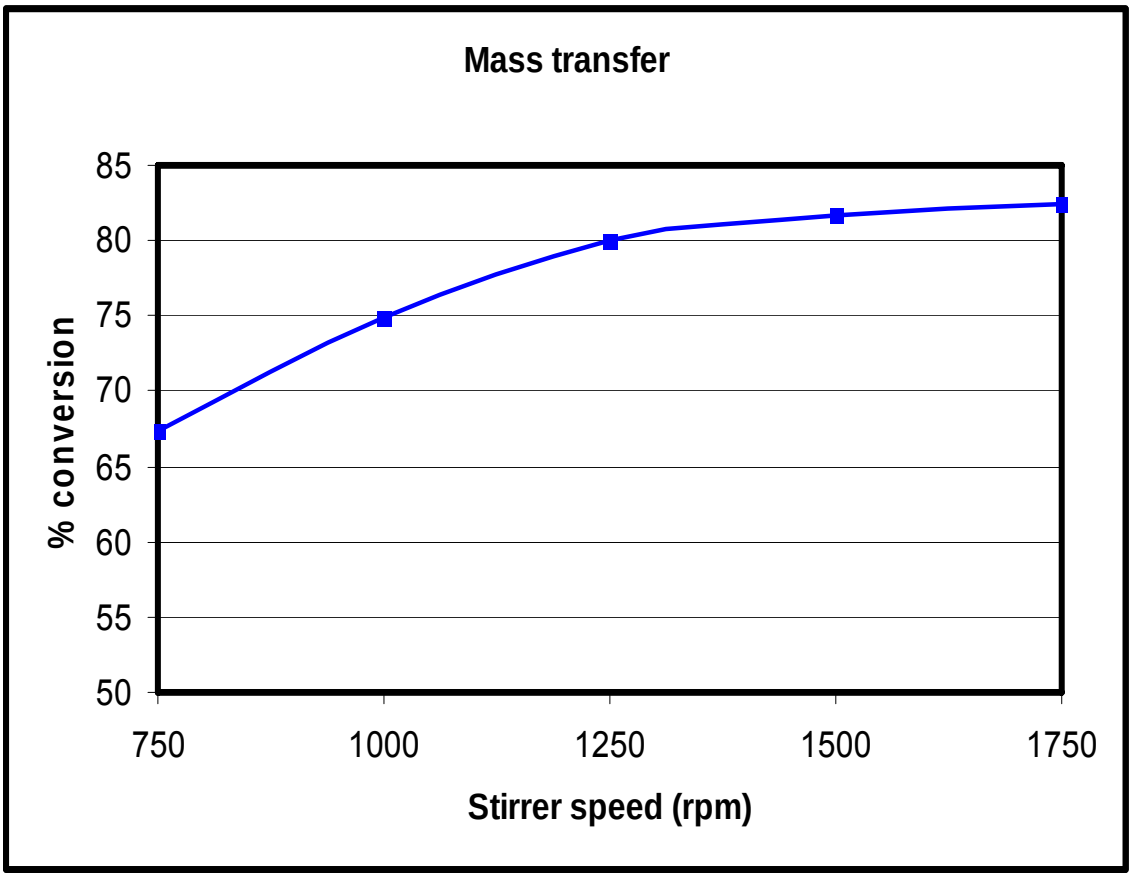


Figure 2.5: Effect of stirring speed on the conversion of the acid-catalyzed cyclization of citronellal

It can be seen from the above results that the reaction is significantly mass transfer limited below stirring speeds of about 1250 rpm. This observation indicates that efficient mixing of the two reaction phases to maximize the interfacial area between the organic and aqueous layers will be required so as to maximize mass transfer. All further experiments were performed at a stirring speed of 1750rpm or above.

2.3.2. Product distribution diagram

The product distribution diagram depicted in Figure 2.6 shows the formation of a main product, namely PMD, accompanied by isopulegol, the PMD-acetal, formed between PMD and citronellal, and another by-product first thought to be the hemi-acetal

between PMD and citronellal. Careful analysis of the mass fragmentation patterns of the PMD-acetal (IUPAC name: 2-(2,6-dimethylhept-5-enyl)-4,4,7-trimethyl-2H-3,4,5,6,7,8,4a,8a-octahydro-3-oxachromene) and the additional by-product (Figures 2.6 and 2.7, respectively) shows that the by-product is the hydrated form of the PMD-acetal (IUPAC name: 2,6-dimethyl-7-(4,4,7-trimethyl(2H-3,4,5,6,7,8,4a,8a-octahydro-3-oxachromen-2-yl))heptan-2-ol) where the double bond has been hydrolysed under action of the acid catalyst. This hydrolysis would be equivalent to the normal hydrolysis of alkenes in the presence of sulphuric acid, and will only become significant at either high acid concentrations, or high temperatures, or both.[5]

The rates and extent of formation of isopulegol, the PMD-acetal, and the hydrolysed PMD-acetal are significantly slower than that of PMD, and they only start to form once at least some PMD has formed. What is significant from the product distribution diagram is that the conversion of starting material reaches a maximum level of around 94%, after which conversion stops or proceeds extremely slowly.

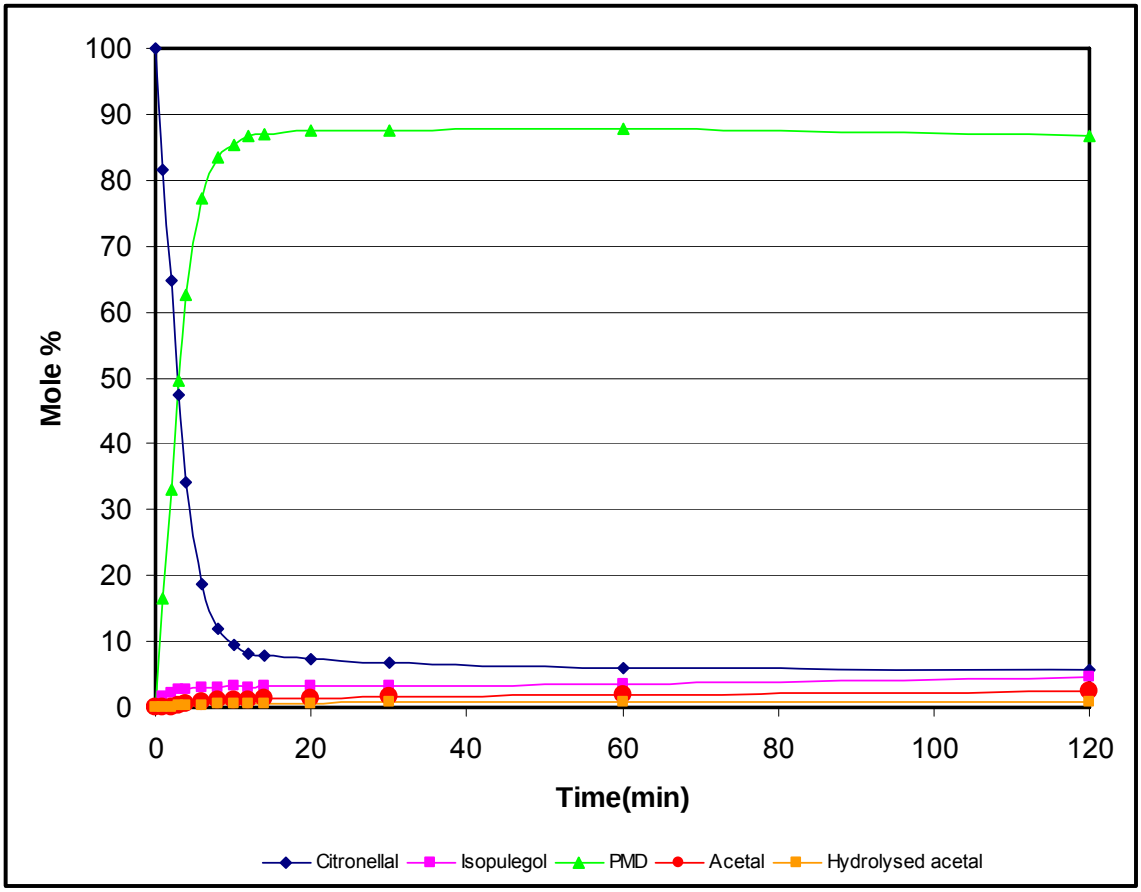


Figure 2.6: Product distribution diagram for the synthesis of PMD from citronellal

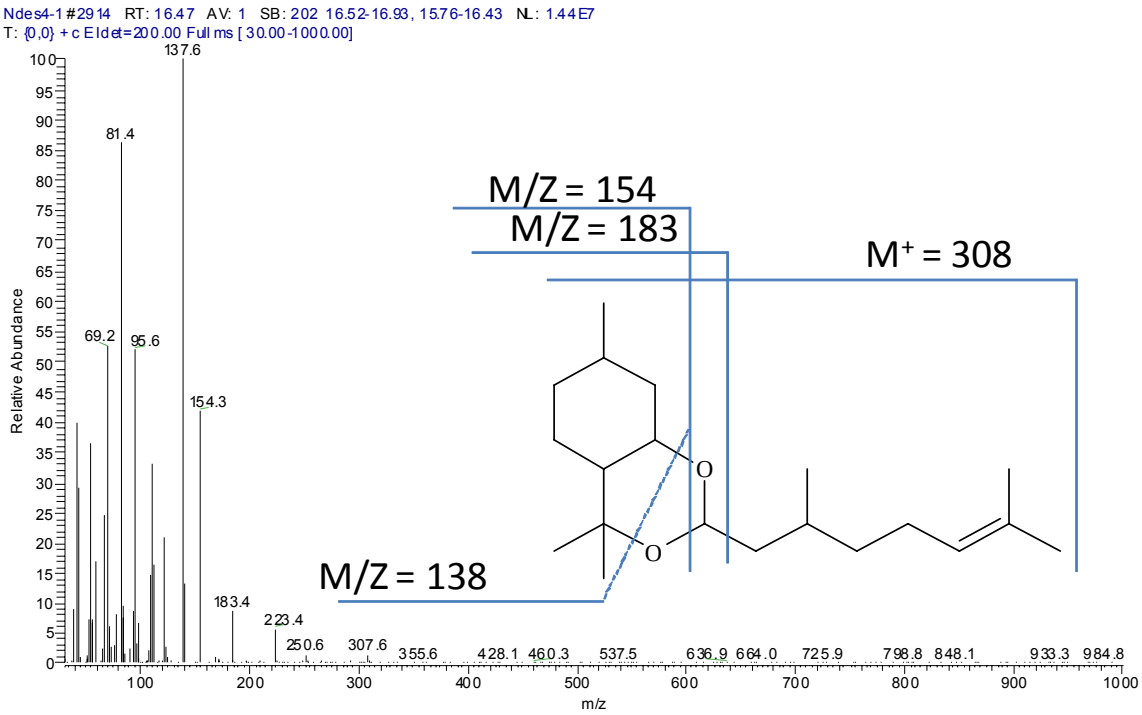


Figure 2.7: Mass fragmentation pattern for PMD-acetal

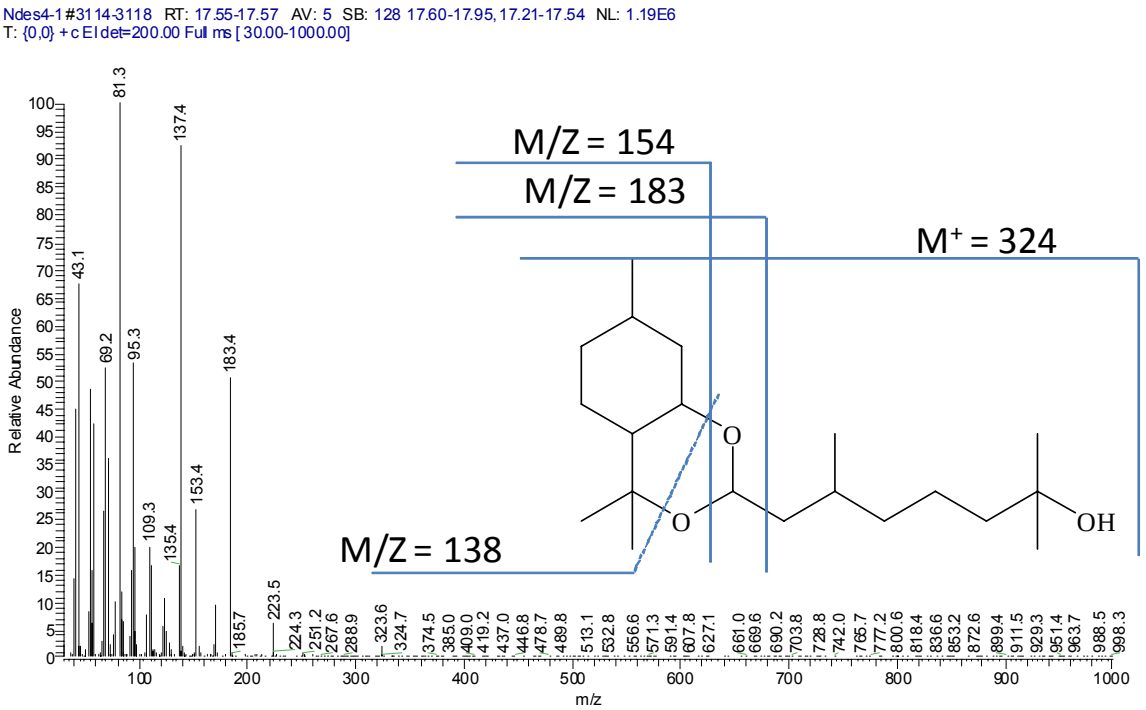


Figure 2.8: Mass fragmentation pattern for hydrolysed PMD-acetal

2.3.3. Selectivity trends

Figure 2.9 illustrates the variation in selectivity to the various reaction components as a function of time, while Figure 2.10 illustrates the selectivity of the same components as a function of the degree of conversion of citronellal. From the plot of selectivity vs. time it can be seen that the selectivity to PMD reaches a maximum of about 94% after which a slow yet consistent decrease in selectivity with increasing reaction time is observed.

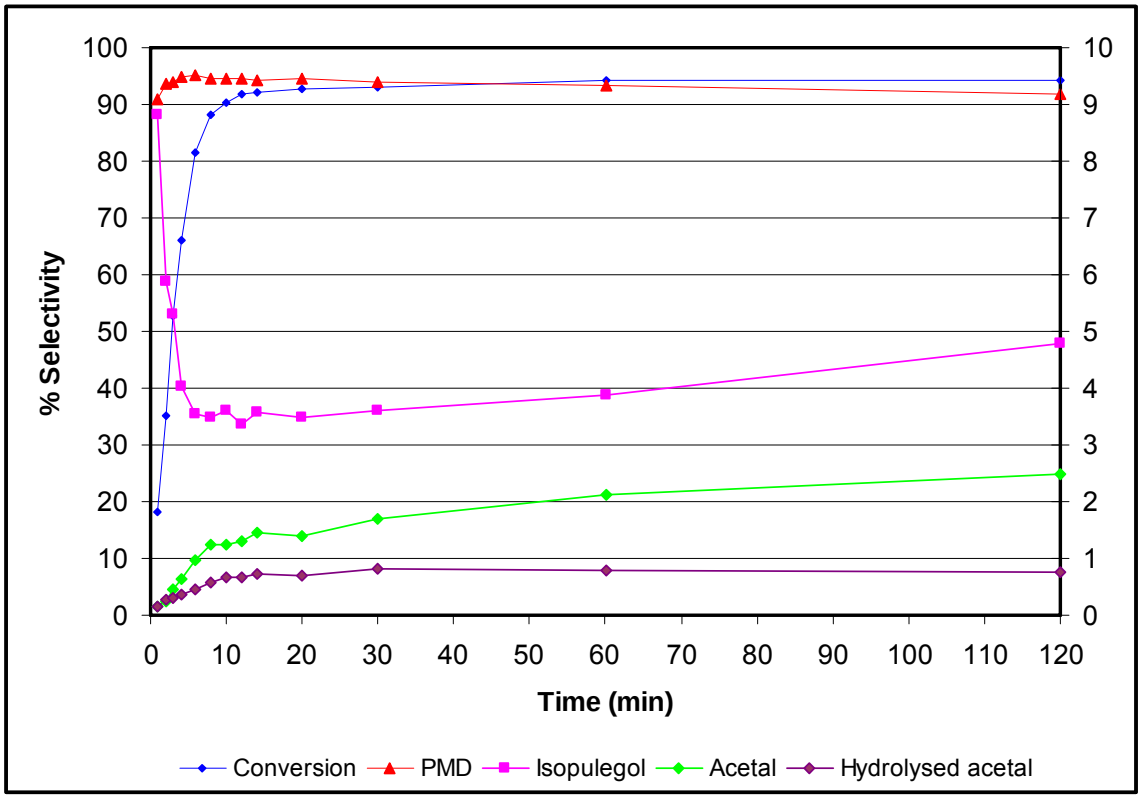


Figure 2.9: Selectivity and conversion as function of time

The selectivity to the hydrolysed PMD-acetal reaches a maximum at around 0.8% and then remains constant. The selectivity to the PMD-acetal, however, continues to increase with increasing reaction time. For isopulegol, selectivity rapidly decreases during the first 6 minutes of the reaction, but then, interestingly, starts to rise again. The selectivity versus conversion plots for the various reaction components (Fig.

2.10) show essentially the same information. However, from this plot it can be seen that PMD selectivity reaches a maximum at a citronellal conversion of about 80%.

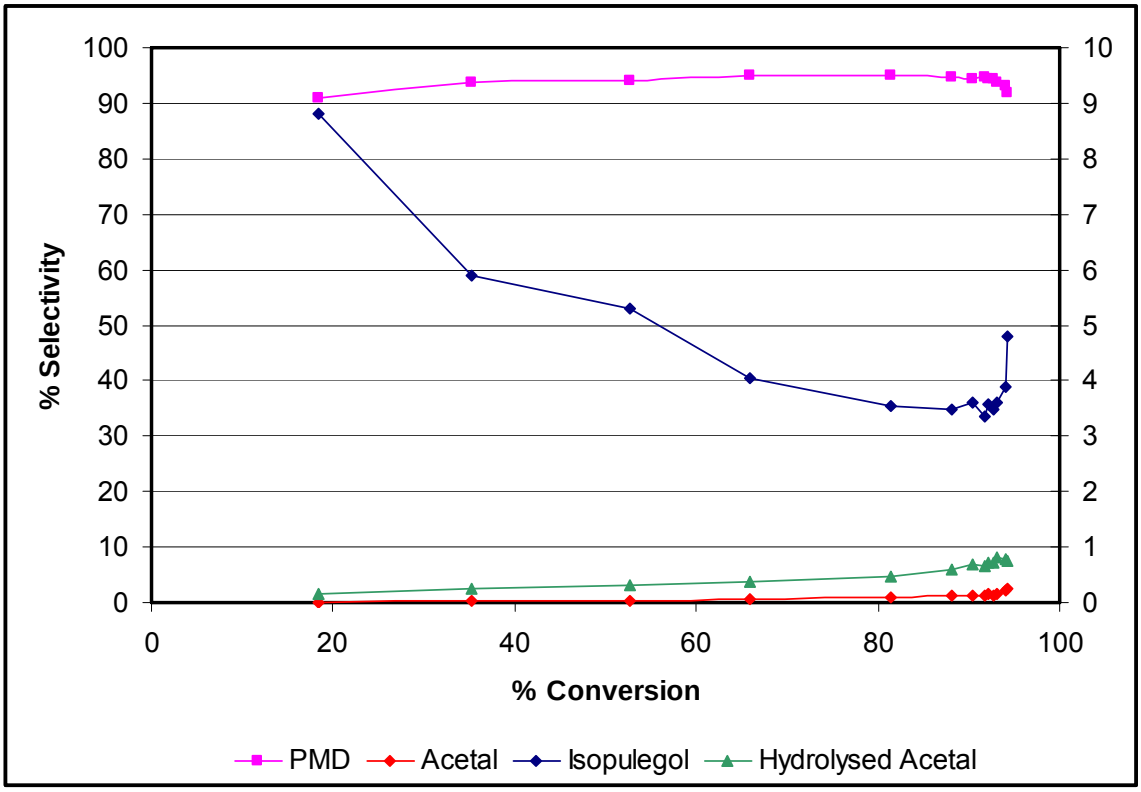
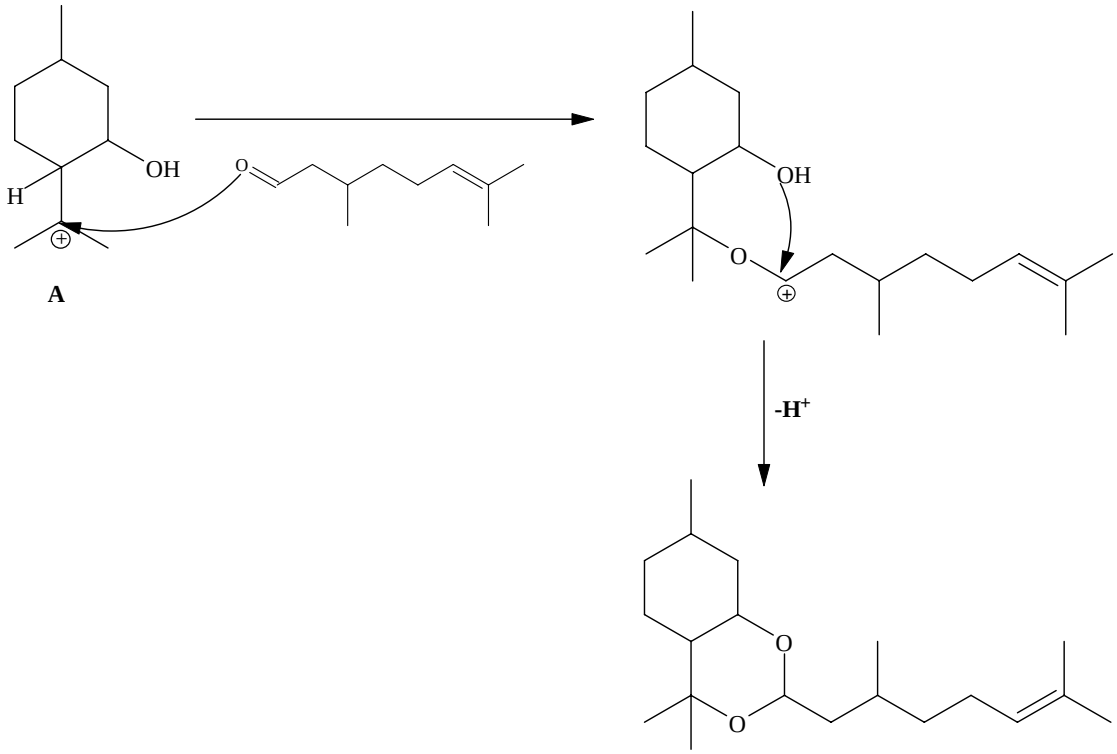


Figure 2.10: Selectivity of reaction components versus citronellal conversion

A number of observations regarding the results described above are worth noting, including:

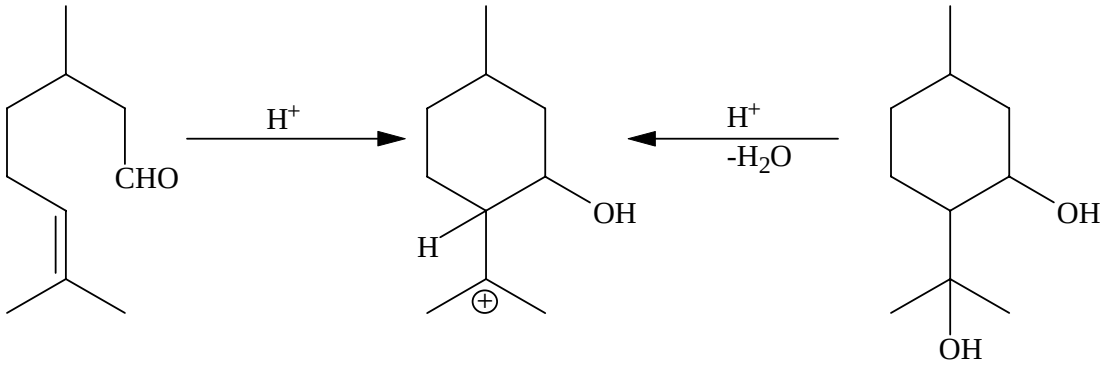
- The sharp decrease observed for the selectivity to isopulegol (Figs. 2.9 and 2.10) suggests that previous suggestions regarding isopulegol being an intermediate in the formation of PMD is probably correct (see Schemes 2.2 and 2.3).
- The increase in isopulegol selectivity at high PMD concentrations (long reaction times), however, suggests that isopulegol is also formed from the PMD product. Such a process is most likely to proceed by means of an acid-catalysed dehydration step (reverse of the process illustrated in Scheme 2.3), a facile process for tertiary alcohols.[6]

- The PMD-acetals are probably formed by reaction of citronellal with the intermediate [A] (5-methyl-2-isopropylcyclohexanol cation - Scheme 2.2) and not by reaction with PMD itself (as proposed previously in Scheme 2.4). This proposal is illustrated below in Scheme 2.5 and is equivalent to the well-known acetal formation reactions for intermolecular Prins reactions.[7]



Scheme 2.5: PMD-acetal formation via intermediate A

It should be noted that the 5-methyl-2-isopropylcyclohexanol cation will appear as intermediate during the cyclization of citronellal, as well as during the dehydration of PMD to isopulegol (Scheme 2.6). As a result, one may expect that the PMD selectivity may tend to decrease over extended reaction periods, while at the same time the PMD-acetal selectivity may increase.



Scheme 2.6: Formation of the 5-methyl-2-isopropylcyclohexanol cation

- The increase in PMD-acetal selectivity with increasing citronellal conversion (Fig. 2.10) appears to follow a logarithmic trend so that the rate of increase in PMD-acetal selectivity becomes quite rapid after PMD selectivity has reached the 50% level. This observation appears to be consistent with the preceding proposals regarding the formation of the PMD-acetals from the 5-methyl-2-isopropylcyclohexanol cation as the instantaneous concentration of the intermediate cation is expected to increase somewhat at higher PMD concentrations due to the dehydration reaction to isopulegol. This is illustrated in the following table where pure PMD (100%) was stirred up in a batch reactor at 85° and a stirring rate of 1750rpm for 30mins.

Table 2.7: Formation of isopulegol from pure PMD

Component	Pure PMD	After reaction
PMD (%)	100	97.2
Isopulegol (%)	0	2.8

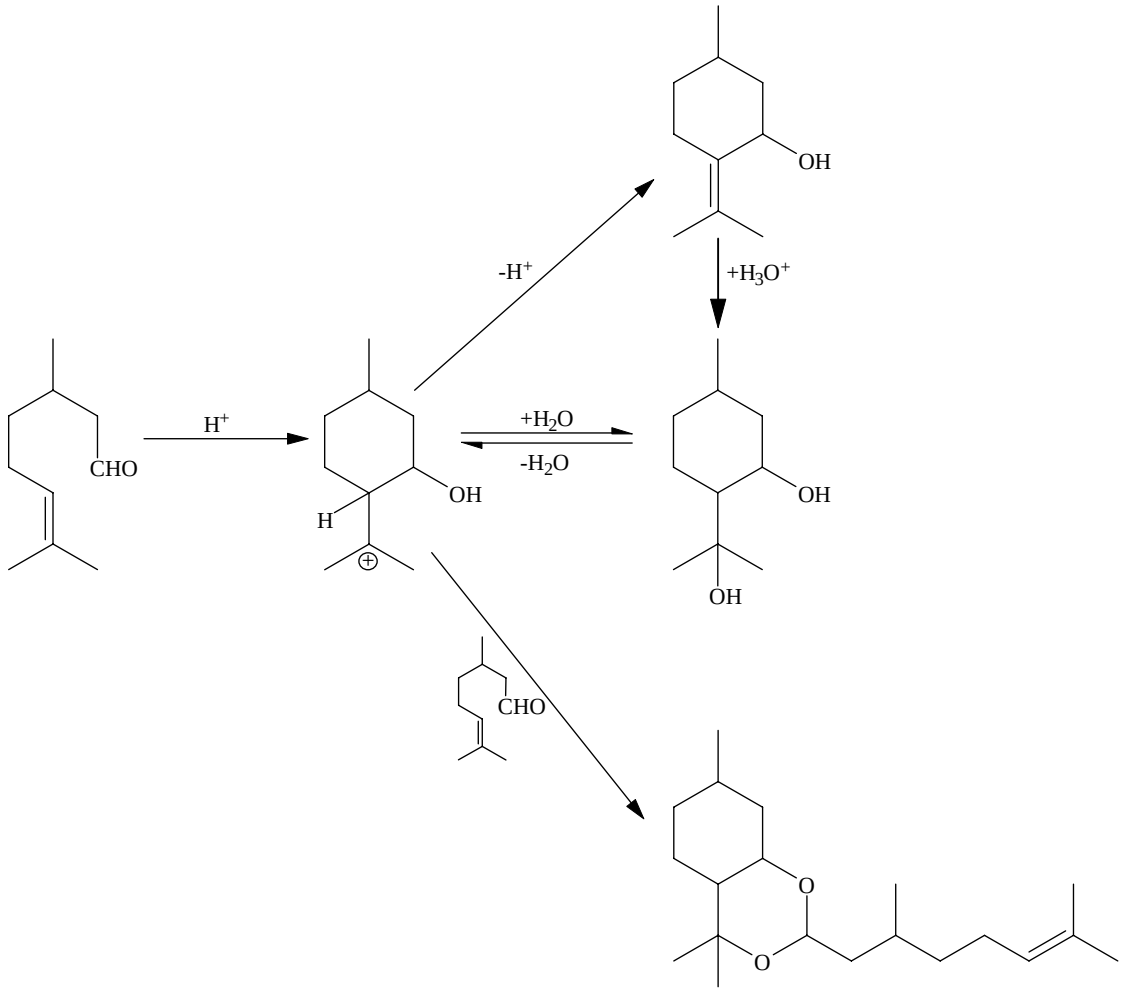
2.3.4. Kinetic investigations

The determination of the intrinsic kinetics of a chemical reaction system is an important first step in chemical reactor development. A thorough knowledge of the kinetic equations in general allows the accurate modelling of reactor types and performance.

In the case of the acid-catalysed conversion of citronellal to PMD, the kinetics of the chemical system is complicated by a number of secondary reactions. Thus, apart from the main reaction, namely the conversion of citronellal into PMD, one also needs to consider:

- The conversion of some citronellal, via the 5-methyl-2-isopropylcyclohexanol cation, into PMD-acetal;
- The conversion of PMD into PMD-acetal; and
- The conversion of PMD into isopulegol.

These interrelated reactions may be summarised as shown in Scheme 2.7.



Scheme 2.7: Main reactions during the synthesis of PMD from citronellal

From the above it can be seen that the kinetic model for the reaction will be complicated, especially at high citronellal conversions when the equilibrium reaction between PMD and isopulegol, as well as the consecutive side reaction resulting in the formation of the PMD-acetal become significant.

These expectations are clearly confirmed by the results of some preliminary kinetic studies. Thus, at citronellal conversions up to about 80%, the reaction obeys pseudo-first order kinetics. This conclusion assumes that the concentration of water in the organic phase will not change due to the efficient mass transfer from the aqueous phase into the organic phase, and due to the very large excess of water present in the reaction system. Under these conditions, and since there are no streams entering

or leaving the reactor, the rate equation may be simply written as (where [C] represents the citronellal concentration):

$$-\frac{d[C]}{dt} = k_1[C] \qquad [2.6]$$

Integration of Eq. [2.6] for a first order dependence on citronellal concentration results in Eq. [2.7], while integration for second order dependence on citronellal concentration results in Eq. [2.8].

$$\ln\frac{[C]_0}{[C]} = k_1 t \qquad or \qquad \frac{[C]}{[C]_0} = e^{-k_1 t} \qquad [2.7]$$

$$\frac{[C]}{[C]_0} = \frac{1}{1 + k_2[C]_0 t} \qquad [2.8]$$

Using the experimental data for the conversion of citronellal up to a conversion level of about 80 mol% (Figure 2.9) and plotting [C] vs time (Figure 2.11), ln [C] vs time (Figure 2.12) and 1/[C] vs. time (Figure 2.13) clearly show that the reaction (up to a conversion level of around 80mol%) is first order with respect to citronellal. This finding is in full agreement with other reported kinetic studies of intermolecular Prins reactions where first order dependence upon aldehyde concentration has been reported.[8]

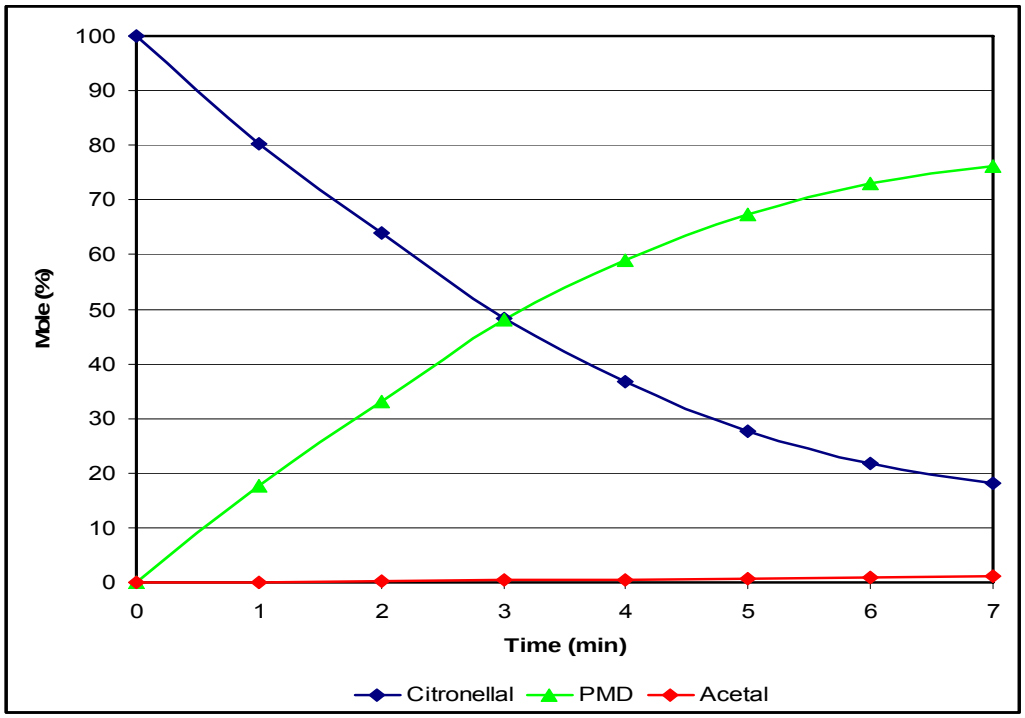


Figure 2.11: Mass distribution of citronellal, PMD and PMD-acetal from 0 to 7 minutes

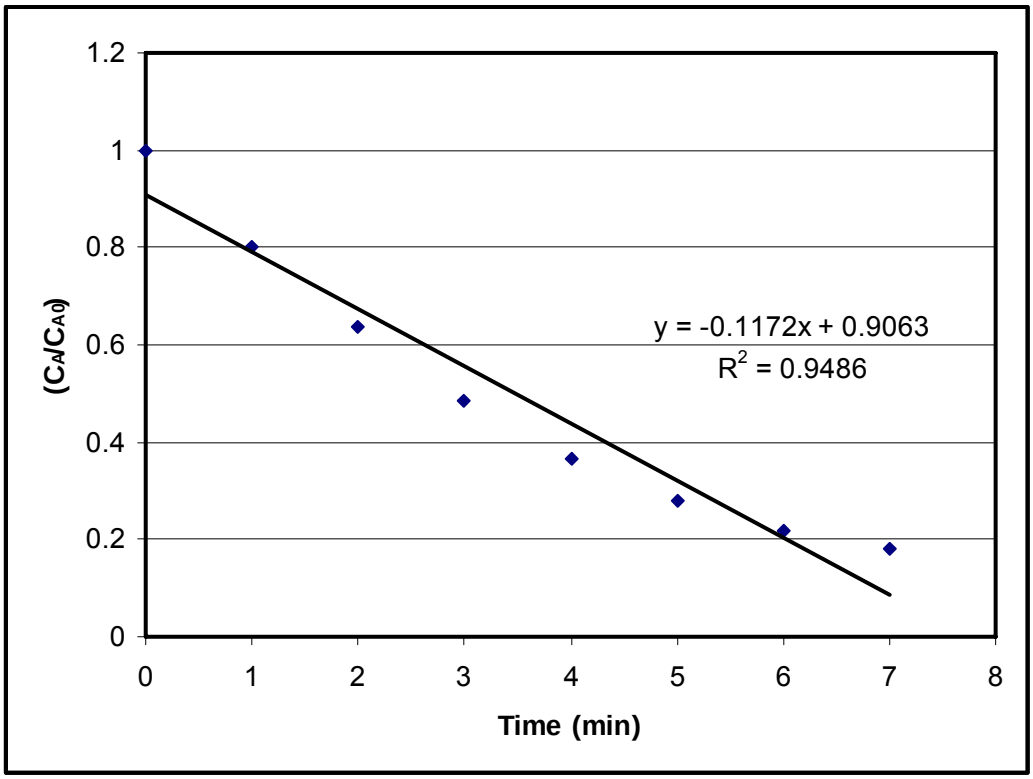


Figure 2.12: Plot of [C] vs time for zero order kinetics

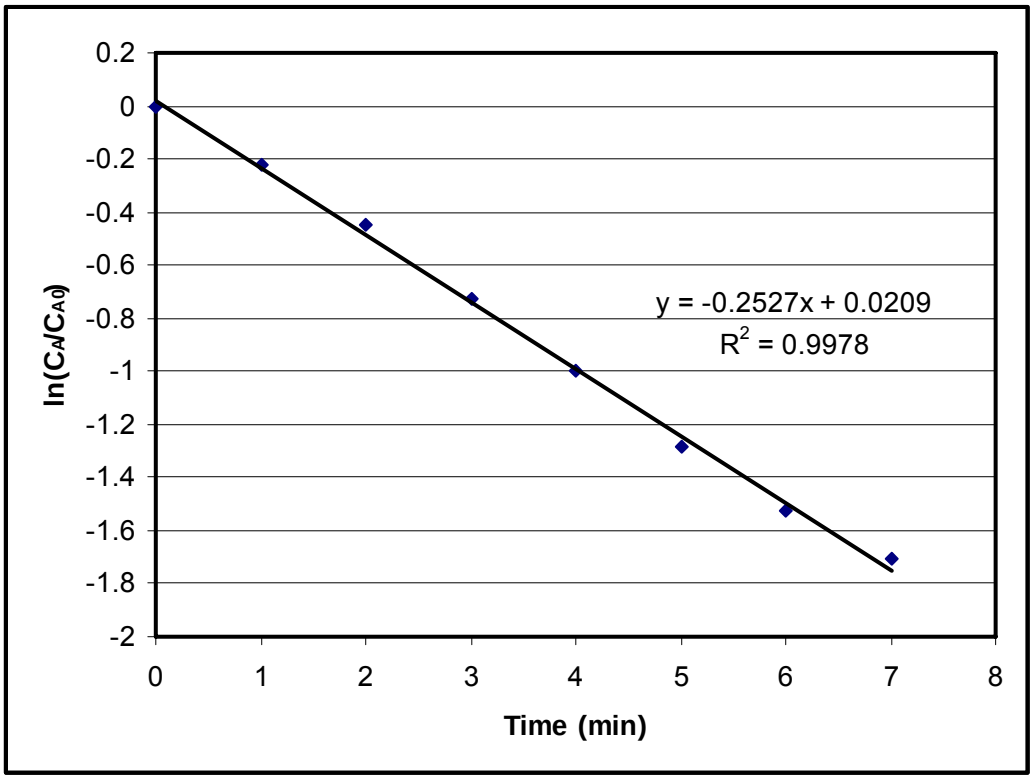


Figure 2.13: Plot of ln [C] vs time for 1st order kinetics

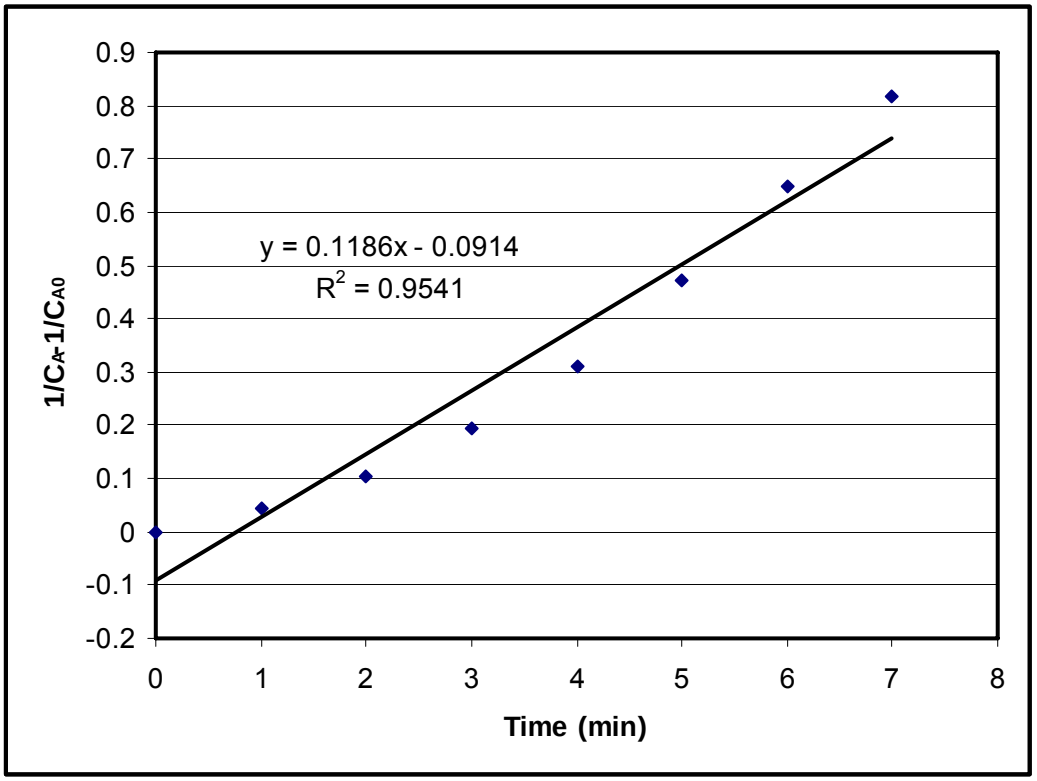


Figure 2.14: Plot of 1/[C] vs time for 2nd order kinetics

The first order rate constant can be estimated from the slope of the straight line in Figure 2.13 and was found to be:

$$k_1 = -0.2527 min^{-1}$$

In order to establish whether the cyclization reaction of citronellal obeys the Arrhenius law and in order to estimate the activation energy for the reaction, the synthesis reaction was repeated at several temperatures ranging from ambient to 85°C, whilst keeping all of the other reaction variables such as stirring speed (1750rpm), citronellal starting concentration (5.52M), and reaction time (7min) constant. Figure 2.14 summarises the results obtained in terms of the relative amounts of citronellal, PMD and PMD-acetal.

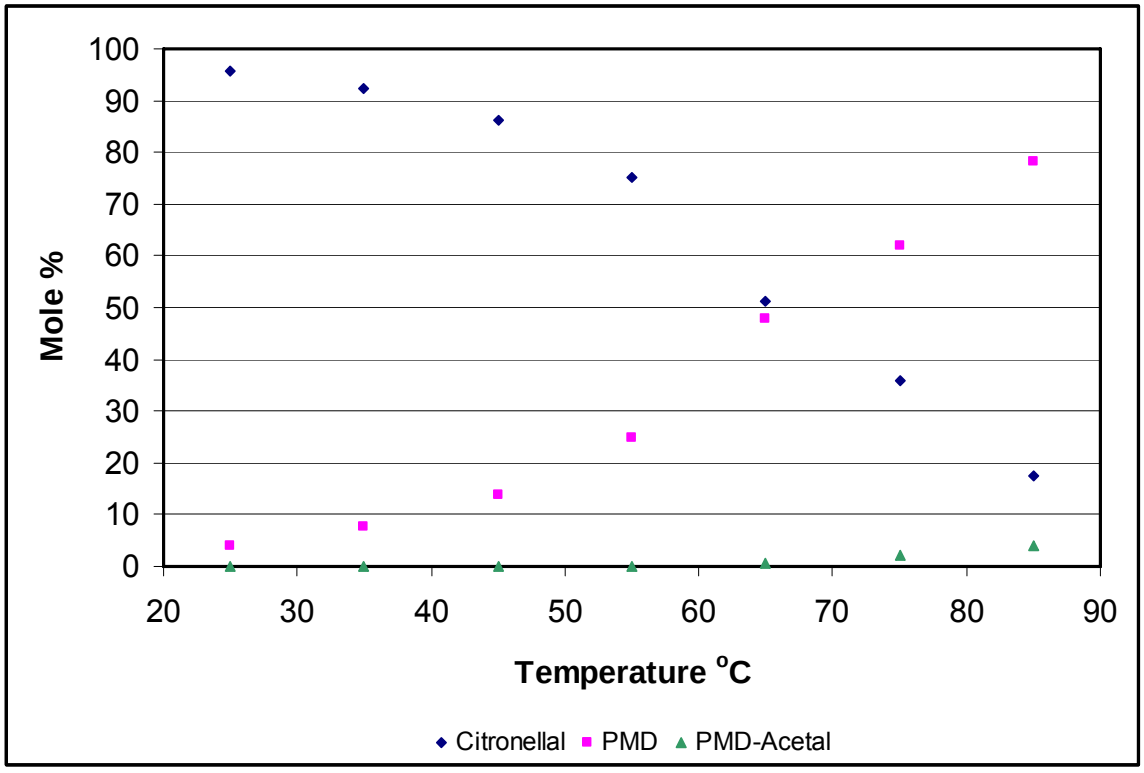


Figure 2.15: Product composition in the organic phase after a reaction time of 7 minutes as a function of the reaction temperature.

The variation of the reaction rate constant "k_1" with temperature can be estimated from the conversion data presented above by using Eq. [2.7]. The results obtained are summarized in Table 2.8.

Table 2.8: Variation in the 1st order rate constant (k_1) with temperature

Temperature (°C)	**25**	**35**	**45**	**55**	**65**	**75**	**85**
$\ln = \frac{[C]}{[C_0]}$	-0.0425	-0.0784	-0.1495	-0.2845	-0.666	-0.10233	-1.7386
k (min^{-1})	0.00607	0.0112	0.02136	0.04065	0.09514	0.14619	0.2527

According to the Arrhenius equation (Eq. [9]), a plot of ln k_1 vs 1/T (Figure 2.15) should give a straight line with slope equal to –Ea/R and y-intercept equal to A.

$$k_1 = Ae^{-Ea/RT} \qquad [2.9]$$

(where k_1 = First order rate constant (min^{-1}); A = Pre-exponential factor (min^{-1}); Ea = Activation energy (j mol^{-1}); R = Gas constant; and T = Temperature (K).)

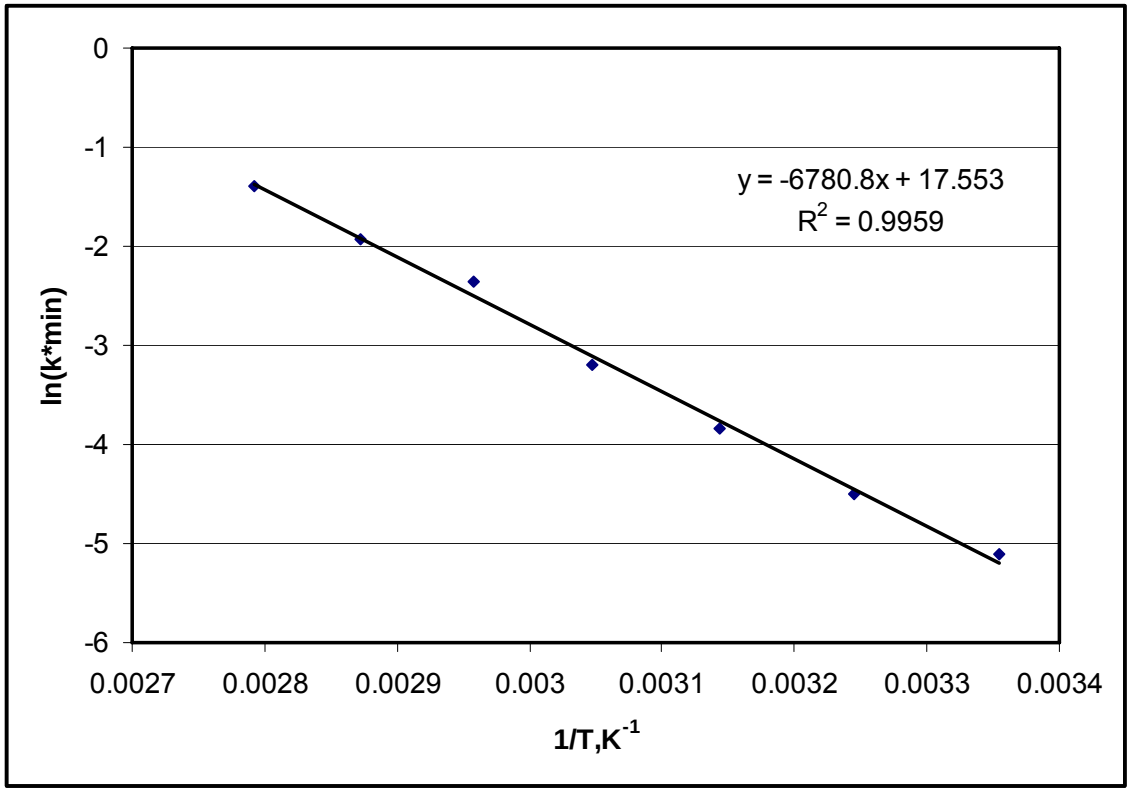


Figure 2.16: Plot of ln k_1 vs 1/T

The plot in Figure 2.16 shows that the Arrhenius equation is obeyed and:

E_a = 56.38 kJmol^{-1}; and
A = 3.98 x 10^7 min^{-1}.

During the acid-catalyzed cyclization reaction of citronellal to PMD, a competitive consecutive reaction occurs to form the PMD-acetal by-product. Since limiting the extent of PMD-acetal formation is important in meeting final product specifications, it is important to understand the mechanism of by-product formation. In an attempt to determine which species play a role in the formation of the PMD-acetals, as well as the order with respect to these species, the method of initial rates for determining the order of the reaction was investigated. From Scheme 2.7 we made the assumption that the reaction can be written in terms of citronellal and PMD (assuming that the

dehydration of PMD also leads to the formation of the 5-methyl-2-isopropylcyclohexanol cation intermediate).

$$C + P \longrightarrow PA$$

(Where C = citronellal; P = PMD; and PA = PMD-acetal)

Thus the rate law for PMD-acetal formation would be:

$$R = k_y[C]^n[P]^m \qquad [2.10]$$

A few experiments were conducted whereby the initial concentrations of citronellal and PMD were varied in order to determine the partial orders with respect to citronellal and PMD. These experiments were carried out by reacting mixtures of citronellal and PMD in the presence of aqueous acid catalyst (0.3%v/v H_2SO_4) at a temperature of 85^oC and at a stirring rate of 1750rpm. The initial rate of PMD-acetal formation was measured as the average rate of PMD-acetal formation over the first 2 minutes of each reaction. Table 2.9 summarises the concentrations of citronellal and PMD used during these reactions, and also lists the initial rates of PMD-acetal formation measured.

Table 2.9: PMD-acetal formation – Initial rates

	Citronellal (mol.L^{-1})	**PMD (mol.L^{-1})**	**Initial rate (mol.s^{-1})**
Run 1	2.77	2.47	15.4 x 10^{-5}
Run 2	2.77	1.48	3.87 x 10^{-5}
Run 3	3.30	1.48	4.52 x 10^{-5}

The partial orders with respect to citronellal and PMD can easily be determined from the data above by inspection. For example, when the concentration of the citronellal is increased (by a factor of about 1.2) whilst keeping the PMD concentration constant (runs 2 and 3), the initial rate of formation of PMD-acetal also increases by a factor of about 1.2. This implies that the partial order with respect to citronellal is zero since the rate remains practically unchanged. However, when the concentration of the PMD is increased (by a factor of about 1.7) whilst keeping the citronellal concentration constant (runs 1 and 2), the initial rate of PMD-acetal increases by a factor of 4. Therefore, the partial order of the reaction with respect to PMD is 2, and provided that other species such as isopulegol is not involved in the formation of PMD-acetal, the overall reaction rate can be written as:

$$\text{Rate} = k_2 [P]^2$$

The above finding could probably be interpreted in terms of the initial dehydration of PMD to form the 5-methyl-2-isopropylcyclohexanol cation intermediate as proposed in Scheme 2.6, since it is difficult to see how two PMD molecules can interact to form the PMD-acetal.

To solve for the rate constant, any one or more of the experimental runs can be used to substitute for the rate and the concentrations of PMD. Table 2.10 lists the results of these calculations for the three trial runs.

Table 2.10: Rate constants for PMD-acetal formation

Run	Rate constant	$\frac{1}{M.s}$
1	k_1	2.53×10^{-5}
2	k_2	1.77×10^{-5}
3	k_3	2.06×10^{-5}
Average	k_{avg}	2.12×10^{-5}

2.3.5. Repeatability studies of the lab-scale process

Before scale-up of the lab-process was attempted on pilot scale, it was important to confirm the robustness of the lab-scale process in a series of repeatability studies. These repeatability experiments were carried out as near as possible to the conditions that would maximise PMD selectivity. For this purpose, the optimum conditions previously reported for the lab-scale batch synthesis of PMD[2] were used. Interestingly these conditions matched the results obtained during this investigation closely, since both studies suggest an optimum PMD selectivity at a citronellal conversion level of about 80% (cf. Figure 2.9). These "optimum" conditions used for these repeatability experiments are summarised in Table 2.11. Four experimental runs were conducted at these conditions and the results obtained are summarised in Table 2.12.

Table 2.11: Batch conditions for maximum PMD selectivity

Optimum Conditions			**Predicted Response**		
Constants		**Variable**			
[H_2SO_4] (%)	**Aq/Org Ratio**	**Temperature ^0C**	**Citronellal (%)**	**PMD (%)**	**Acetal (%)**
0.3%	4:1	85	21.91	75.85	1.43

Table 2.12: Robustness testing of lab-scale batch process

Run	Citronellal (%)	Isopulegol (%)	PMD (%)	Acetal (%)
1	17.39	4.51	76.78	1.32
2	18.26	4.52	76.00	1.22
3	18.25	4.07	76.38	1.30
4	18.66	3.97	75.97	1.40
Average	**18.14**	**4.27**	**76.28**	**1.31**
Std. Dev.	**0.53**	**0.29**	**0.38**	**0.07**
Lower limit*	**17.29**	**3.81**	**75.68**	**1.28**
Upper limit*	**18.99**	**4.73**	**76.88**	**1.34**

**at the 95% confidence level*

From the above results, it can be seen that the lab-scale batch process can be repeated with fairly large precision over several runs. At these conditions the conversion of citronellal obtained is about 82% and the selectivity to PMD is about 93%. It is also important to note that the amount of PMD-acetal exceeds the target limits set for PMD-acetals (< 1.0%).

2.3.6. Pilot plant scale-up of batch process

For the scale up of the lab-scale batch process for the synthesis of PMD, certain procedures used for the laboratory-scale batch process had to be revised due to practical limitations on the pilot plant. For the lab-scale process, pre-heated citronellal (85°C) was added to the pre-heated (85°C) acidic aqueous phase in order to start the reaction. It wasn't possible to preheat the citronellal and add it to heated aqueous medium during the pilot runs as the citronellal was introduced to the reactor from an unheated glass reservoir situated above the reactor. To partially reduce the effect of a significant temperature drop by adding cold citronellal to a heated aqueous phase, it was decided to pre-heat the aqueous and organic phases together in the

reactor vessel and then add the catalyst (diluted slightly) after the reactor contents had reached the desired reaction temperature. This approach was first tested at the bench scale before any runs were conducted at the pilot scale. These experimental lab runs showed that the same reaction performance and product qualities could be maintained.

Table 2.13: Comparison between the normal batch procedure and addition of the catalyst to the reaction mixture after preheating

	Baseline reaction	**Addition of catalyst after preheating**
Citronellal (%)	18.73	18.33
Isopulegol (%)	3.89	3.81
PMD (%)	75.95	76.52
PMD-acetal (%)	1.43	1.34

The process flow diagram for the pilot-scale experiments is illustrated diagrammatically in Figure 2.17.

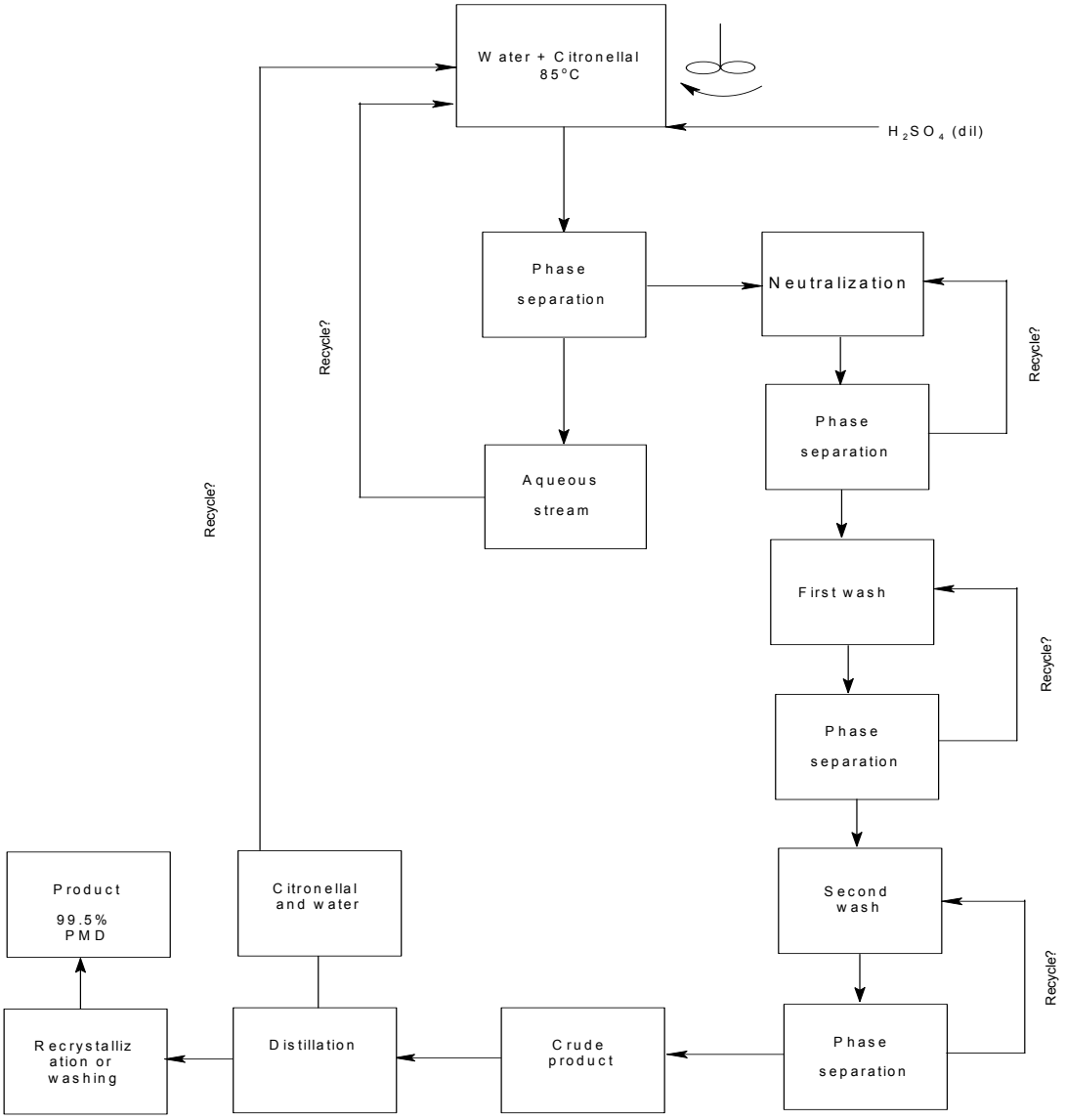


Figure 2.17: Process flow diagram for PMD synthesis at the pilot scale

The first 30L scale-up run was performed by replicating the experimental conditions of the “optimum” lab-scale batch process, except for the change in the catalyst addition method described before. Table 2.14 shows the experimental conditions used and the results that were obtained from trial run No. 1.

Table 2.14: Experimental conditions and results for first 30L scale-up run

Reactor size	Time (min)	Temp. (°C)	Conversion (%)	Citronellal+ isopulegol (%)	PMD (%)	Acetal (%)
0.5L	8	85	81.86	18.14	76.28	1.31
30L	8	85	48.69	51.31	47.38	0.76

The results depicted above clearly show a significant decrease in the citronellal conversion in the 30L Büchi reactor when the same settings as the laboratory batch reaction were used. This result was not too surprising in view of the expected difference in mass transfer between the two reactor systems. It should be noted that it was not possible to replicate the degree of mixing in the 30L reactor due to the difference in impellers used for the lab-scale and pilot reactor, and also due to the fact that the rate of stirring (rpm) could not be measured on the pilot reactor. The amount of PMD-acetals formed during trial run 1 is, however, comparable to the amount of PMD-acetals expected for a bench scale reaction restricted to a 48% conversion (cf. Figure 2.10).

In the next series of reactions on the 30L Büchi reactor, the effect of reaction time on the conversion and selectivity at the 30L pilot scale was investigated. During these experiments, all the other reaction conditions were kept exactly as for trial run 1 (Table 2.14). The results obtained for these runs are summarized in Table 2.15.

Table 2.15: Effect of reaction time on citronellal conversion and PMD selectivity - 30L reactor

Trial Run	Reaction time	Agitator speed	Conversion (%)	Citronellal (%)	PMD (%)	Acetals (%)
1	8	4	48.69*	51.31	47.38	0.76
2	16	4	75.61*	47.21	26.40	2.0

**** Calculated via the amount of starting material stripped from the reaction mixture by distillation***

Increasing the reaction time from 8 to 16 minutes increases the citronellal conversion from about 48% to about 75%. At the same time, the PMD selectivity is decreased from about 97% to about 94%, while the amount of PMD-acetals formed is increased more than 3-fold to about 2.6%. These observations again point to significant differences in mass transfer (degree of mixing) between the reactor systems.

Table 2.16 shows the results obtained at two different stirring speeds of the agitator on the 30L Büchi reactor. When comparing runs 1 and 4, one notices that increasing the agitation on the 30L reactor has no significant influence on the reaction performance. At this point it should be mentioned that the 30L Büchi reactor has no internal mixing baffles, which means that a higher stirring speed does not necessarily translate into a better degree of mixing.

Table 2.16: Effect of increased agitator speed

Run	Reaction time	Agitator speed	Conversion (%)	Citronellal (%)	PMD (%)	Acetals (%)
1	8	4	48.69*	51.69	47.38	0.76
4	8	7	48.97*	51.03	48.26	0.71

**** Calculated via the amount of starting material stripped from the reaction mixture by distillation***

Takasago reported their intentions to produce PMD using a batch process involving the slow, semi-batch addition of starting material to the aqueous catalyst solution at low (~55^{o}C) temperatures so as to minimize the formation of the by-product, PMD-acetals.[1] It was therefore decided to investigate this approach on the 30L scale so as to evaluate the potential of minimizing PMD-acetal formation. Table 2.17 summarizes the results obtained for the slow addition of citronellal at two different reaction temperatures.

Table 2.17: Effect of temperature and addition rate on reactor selectivity

Run	Addition time	Agitator speed	Temp. (°C)	Conversion (%)	Citronellal (%)	PMD (%)	Acetals (%)
5	60	5	65	72.81	27.17	67.16	3.44
6	60	5	85	86.83	13.17	78.10	5.39

The above results show that the slow addition of starting material does not decrease the extent of PMD-acetal formation. On the contrary, the effect of the extended reaction times under these conditions has the effect of significantly increasing the extent of PMD-acetal formation compared to the previous trial runs.

2.4. Concluding remarks

Several aspects of the findings described in this chapter are important for the further development of a commercial process for the synthesis of PMD by means of the acid-catalysed cyclization of citronellal. These include:

- The cyclization reaction is first order with respect to citronellal and obeys the Arrhenius equation. This implies that performing the synthesis in the absence of a reaction solvent (e.g., to improve mass transfer) would be desirable, and

also that an increase in reaction temperature can significantly reduce reactor residence times (and consequently the final reactor size).

- Towards high citronellal conversions, several side reactions become significant which complicate the kinetic model for the reaction. These side reactions include the dehydration of the PMD product under acid-catalysis, essentially setting up an equilibrium between PMD and isopulegol and the reaction of the starting material with an activated intermediate, most probably the 5-methyl-2-isopropylcyclohexanol cation, to form PMD-acetals.
- The 5-methyl-2-isopropylcyclohexanol cation intermediate can be formed both directly from citronellal during the cyclization reaction, and from PMD during its dehydration to isopulegol. This implies that the rate and extent of PMD-acetal formation will increase at higher PMD concentrations (or alternatively, higher citronellal conversions).
- The rate of PMD-acetal formation appears to be second order with respect to PMD concentration which explains the increasing rate and extent of PMD-acetal formation towards high citronellal conversions. In addition, it also explains the increase in PMD-acetal formation with longer reactor residence times. This implies that for further development work, restricting both the citronellal conversion and limiting the reactor residence time would be important.
- The reaction has been shown to be affected by the degree of mixing (mass transfer) between the aqueous and organic phases. Maximising the degree of mixing, hence mass transfer, will therefore be important to achieve short reactor times and achieve desired selectivities.
- Preliminary scale-up tests of the batch synthesis process has demonstrated the difficulty of achieving desired processing parameters such as a desired degree of mixing and effective reagent dosing. The results obtained from these trial scale-up runs indicate that achieving both a high throughput, as well as desired product specifications will not be easily achieved using a batch process.

2.5. References

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Chapter 3

Synthesis of p-menthane-3,8-diol: micro-reactor studies

Abstract

The synthesis of p-menthane-3,8-diol was studied using a commercially available micro-structured reactor in order to determine whether it is possible to perform the PMD reaction as a continuous process. The results obtained showed that the use of a micro-mixer such as the caterpillar micro-mixer did not provide enough residence time in order for desirable conversions (≈40%) to be obtained. By combining the micro-mixer with delay-loops of different thicknesses and lengths with increasing reaction temperatures it was shown that the conversion of citronellal could be improved to some extent, but compared poorly to the expected conversions for a well-stirred batch reactor. By packing selected delay loops with inert SiC particles, improved mass transfer was observed between the organic and aqueous phases as reflected in the increased conversion of citronellal. Despite the fact that the packed tubes were still operating in a mass transfer limited domain, increasing the reaction temperature (and consequently the pressure) to 115^{o}C resulted in conversion levels far exceeding what could be achieved at the "optimum" batch reactor conditions at comparable residence times. It was also shown that replacing the caterpillar micro-mixer with a commercially available T-piece did not affect the results due to the continuous mixing of the reaction phases in the packed tube.

3.1. Introduction

The use of micro-structured reactors for chemical synthesis offers specific advantages over conventional batch reactors. These advantages include improved heat transfer and mixing, and also products with improved physical qualities such as consistent particle size. Operating parameters such as temperature, residence time, and flow rates are more easily controlled in reactions that take place in a small volume. It is also the small volumes of these reactors which result in an intrinsic process safety. Micro-structured reactors can be used as process engineering tools for acquiring information, which allows, in a short time and with greater safety, a process to be transferred from lab-scale to the pilot or production scale.

The advantages of micro-structured reactors have been demonstrated with great success for well known reactions such as the Wittig, Knoevenagel, Aldol, Ugi and Suzuki reactions, to name but a few.[1] Many types of micro-structured reactors have been reported for use with liquid-phase reactions, gas-liquid reactions, photochemical, electrochemical and also gas-phase reactions. In many liquid-phase systems, micro-structured reactors, or micro-mixing devices to be more correct, are combined delay loops to increase residence times for reactions which have slower kinetics. The use of packed delay loops with solid catalyst particles in two-phase liquid systems have been reported.[2,3] These delay loops are commonly regarded as plug flow reactors. Fluid flowing through such a reactor may be modelled as an infinitely thin coherent "plug", where the plug is of a uniform composition travelling in the axial direction of the reactor, but with differing composition to the leading and trailing plugs. The required assumption is that as a plug flows through a PFR (plug flow reactor), the fluid is perfectly mixed in the radial direction but not in the axial direction (forwards or backwards). Each plug of differential volume is considered as a separate entity, effectively an infinitesimally small batch reactor, limiting to zero volume. As it flows down the tubular PFR, the residence time of the plug is a function of its position in the reactor. IMM (Institüt für Mikrotechik Mainz) produces a range of commercially available micro-structured reactor systems, including bench-scale

synthesis plants which consist of one or more micro-mixers, delay loops and heat exchanger configurations, which can be used for various applications.[4]

Micro-structured reactors allow for the reactions to be performed in a continuous manner which are in some cases much more beneficial to chemical processing.[5] By using continuous processing, the variance in product quality commonly observed between batches in the fine and pharmaceutical industries can be reduced. There are many good reasons to evaluate the potential advantages of micro-structured reactor technologies, and therefore the synthesis of PMD was evaluated on a commercially available micro-structured organic synthesis bench-scale plant, which consisted of a micro-mixer connected to some delay loops to provide for variable residence times.

3.2. Experimental

3.2.1. Equipment setup

All continuous-flow experiments were carried out on the IMM Organic Synthesis Plant (OSP). The plant consists of two semi-preparative HPLC pumps, two cross flow heat exchangers, a caterpillar micro-mixer (shown in Figure 3.3(a)), four delay loops of different sizes for variable residence times, and a tube-in-tube axial heat exchanger to cool down products before exiting the plant. The cross-flow heat exchangers, micro-mixer and the delay loops are immersed in a hot oil bath, capable of temperatures of up to 200°C. A schematic diagram of the OSP plant is shown in Figure 3.1:

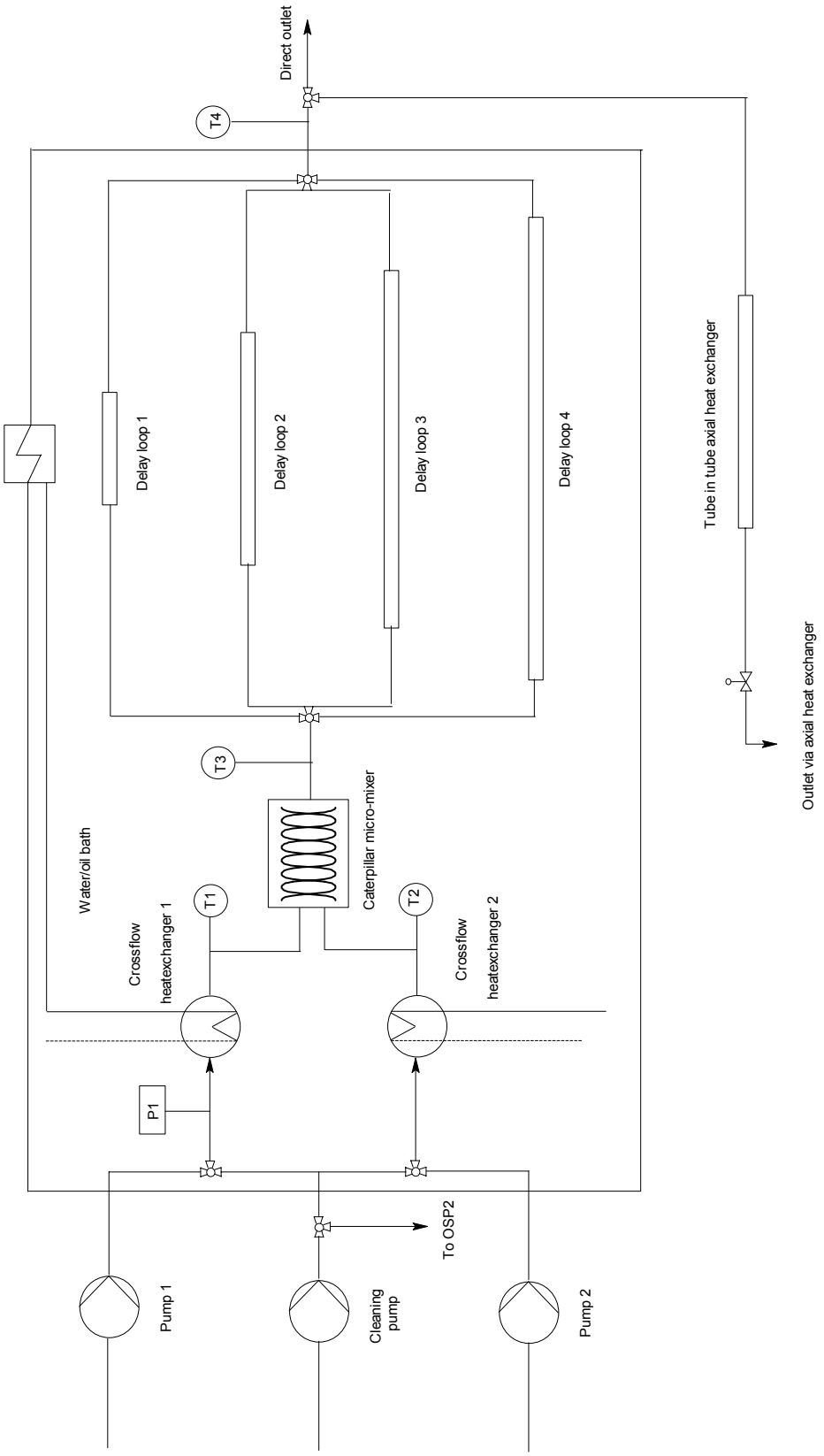


Figure 3.1: A schematic representation of the Organic Synthesis Plant

The HPLC pumps and oil bath of the OSP are controlled via a computer with specially designed software. The software can be used to write programs in order to perform temperature and flow rate stepping, and also allows for data acquisition of relative pressures and temperatures during operations.

The components of the OSP are described below.

3.2.1.1. Cross flow heat exchanger

The cross flow heat exchangers used in this study (Figure 3.2) consist of a stack of laser welded micro-structured plates that allow counter- or co-current flow schemes. They can be used for liquid-liquid, liquid-gas or gas-gas applications and can also serve for evaporation or condensation applications. They are generally much more efficient than conventional heat exchangers due to the low material thickness which they are made of.

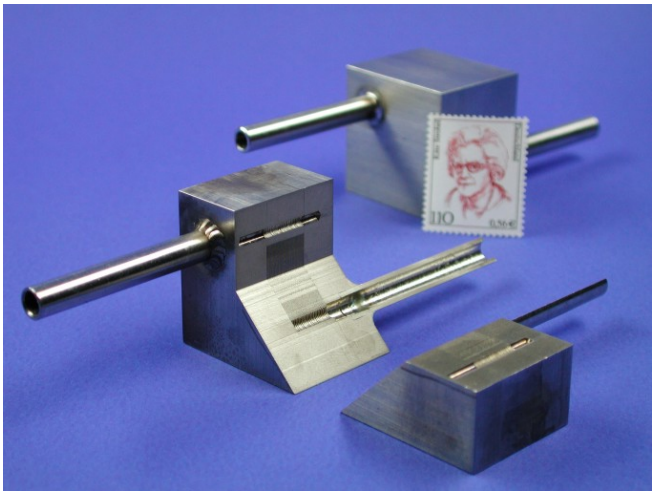
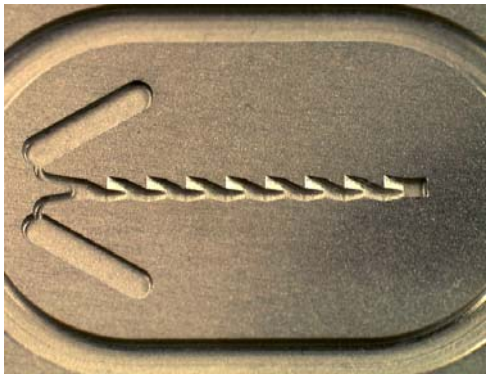


Figure 3.2: The cross-flow heat exchanger

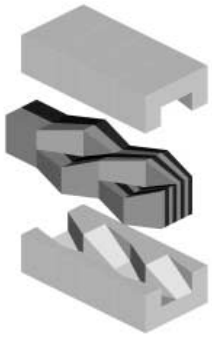
During this study, the cross flow heat exchangers were used to preheat reagents before they enter the micro-mixer or reaction zone.

3.2.1.2. Caterpillar micro-reactor

A caterpillar micro-mixer (Figure 3.3) was used during this study and is generally used in applications where fast mixing at higher throughput is desired, providing high performance for liquid-liquid mixing as well as gas-liquid mixing. Its higher flow rate characteristics enable it to process up to 100 tons of material per annum.



(a)



(b)

Figure 3.3: a) Caterpillar micro-mixer b) "Split and recombine" principle of the caterpillar micro-mixers

This particular mixer uses a "split and recombine" mixing principle shown in Figure 3.3(b). Streams are continuously divided, folded, guided over each other and recombined in every mixing step. Typically these mixers have 8 to 12 mixing steps.

The operating specifications of the CPMM V1.2 - R1200 caterpillar micro-mixer are shown below.

Table 3.1: Operating specifications of the CPMM V1.2 – R1200 micro-mixer

Micro-mixer	CPMM V1.2 – R1200
Temperature range (°C)	-40 to 200
Pressure stability (bars)	100
Flow rate (L/h)	4-80
Residence time (ms)	3.15 – 70.2
Inner volume (µL)	78
Max viscosity (mPas)	100

3.2.1.3. Delay loops

The caterpillar micro-mixer is connected to 4 delay loops (Figure 3.4) of different lengths and diameters (1/8" and ¼"), which allows for variable residence or reaction times for a given set of parameters. These delay loops are connected to one outlet and can be inter-changed by switching a five way valve.

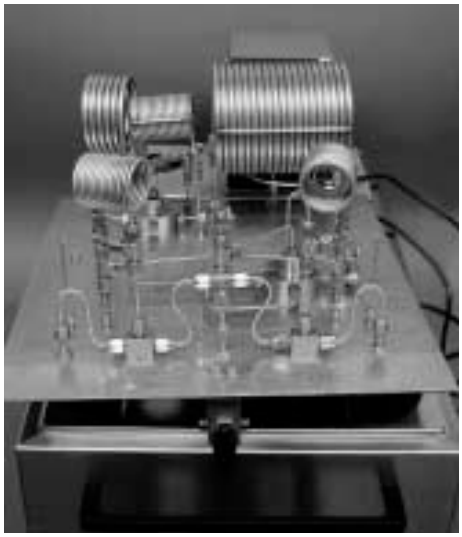


Figure 3.4: The delay loops of the OSP

3.2.1.4. Packed delay loops

During specific experiments, the longest delay loop (6.35mm (OD) x 4.57mm (ID) x 5600mm) was packed with solid SiC (30 Grit) particles to improve mixing of the two reaction phases during these trial experiments (Figure 3.5). 30 Gritt relates to an average particle size of 550microns and the particles used in this study were not sieved before use. The delay loop was removed from the OSP plant and filled with SiC particles which roughly decreased the internal volume of the delay loops by 50%. After the delay-loop was filled with the desired material, 40 micron stainless steel wire mesh was placed at each end of the loop to ensure that the packing material remained stationary within the tube during reactions. After the ends were closed off with wire mesh and swagelok fittings, the loop was placed back into position on the OSP and the respective reactions carried out.

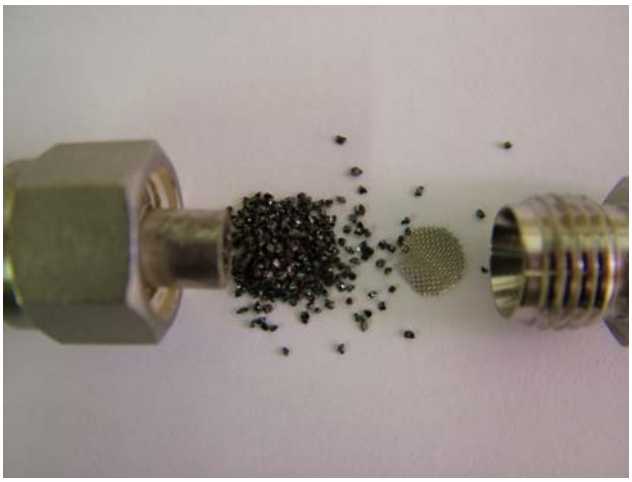


Figure 3.5: The packing material and the wire mesh used for packing of the delay loops

3.2.1.5. Tube-in-tube heat exchanger

The OSP also has the option to cool down products before they exit the plant. By switching a three way valve, the product stream can either exit the plant directly, or be diverted through the heat exchanger to be cooled down. This step is specifically important to reactions where the product stream needs to be cooled down to stop or slow down the reaction, or to prevent vaporization of the respective streams when it exits the plant, especially where the reaction was performed under pressure at temperatures higher than the boiling points (atmospheric) of the respective streams. The tube-in-tube heat exchanger consists of a 3.178mm (OD) tube encased by a 6.35mm (OD) stainless steel tube and is approximately 0.5m long.

3.2.1.6. Needle valve

A needle valve was added at the end of the heat exchanger of the existing OSP in order to perform reactions at elevated pressures. This is not a standard feature of the OSP, but was a necessary adjustment to ensure that the reagents remained in the liquid phase when reactions were performed above the boiling points of respective reagents. The flow coefficient for the reactions that were performed at 65mL/min was calculated to be C_v = 0.002 by using Equation 3.1.

$$Cv = 11.7q\left(\frac{S.G.}{dp}\right)^{\frac{1}{2}} \qquad [3.1]$$

where: *q = water flow (m^3/h)*

S.G. = specific gravity (1 for water)

dp = pressure drop (kPa)

The calculated value was used to select the correct needle valve for the OSP. A commercially available needle valve with a flow coefficient of C_v= 0.004 was used in all the experiments.

3.2.2. Materials

All the materials that were used for the synthesis of p-menthane-3,8-diol, the sources of procurement and the respective grades, are listed in Table 3.2, while the solvents used for analytical purposes are listed in Table 3.3. All materials were used as received unless otherwise specified. The relevant physical properties of the major products formed during the reaction are provided in Table 3.3.

Table 3.2: Reagents for synthesis

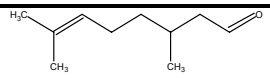
Name	Structure	MM (g/mol)	Supplier	Grade Purity
Citronellal		154.14	Merck	AR
Sulphuric acid	H_2SO_4	98.08	Merck	95-98%
Sodium bicarbonate	$NaHCO_3$	84.01	Saarchem	AR

Table 3.3: Reagents for analysis

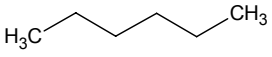
Name	Structure	MM g/mol	Supplier	Grade Purity
n-Hexane		86.1766	Merck	AR
Heptane	isomers	100.21	Merck	AR

Table 3.4: Physical properties of reagents and products

	MM (g/mol)	BP (°C)	Density g/cm^3
Citronellal	154.15	207/760mmHg	0.851
Isopulegol [a]	154.15	212/760mm Hg	0.912
p-Menthane-3,8-diol[b]	172	108°C/0.8mmHg	0.989
p-Menthane-3,8-diol citronellal acetal[c]	308	123-127°C/0.2mmHg	N/A

[a]*Intermediate,* [b]*Product,* [c]*Byproduct*

3.2.3. General procedure for the synthesis of PMD using the OSP

Before any experiments were carried out, water was allowed to run through the OSP as a preliminary flushing-cleaning step. After flushing, the OSP oil bath temperature was set to the desired reaction temperature, whereafter pure citronellal and aqueous sulphuric acid (0.3% v/v) were fed into the OSP using the semi-preparative HPLC pumps. For reactions that were performed at temperatures higher than the boiling point of the aqueous phase, the needle valve at the end of the heat exchanger was adjusted until a back pressure reading of 20 bars was observed. This was to ensure that the aqueous phase would maintain a liquid state during the reactions that were performed above 100°C.

After pressure and temperature stabilization was observed from the measurements taken during operation, a suitable amount of the reaction mixture exiting the OSP was sampled directly into 100mL of a 2.5% sodium bicarbonate solution (room temperature). This was done to neutralize the acid catalyst and quench the reaction. The organic phase of the sample was separated and washed three times with hot

(80°C) DI water, each time discarding the aqueous layer and retaining the organic layer. The organic layer was then dried using anhydrous $MgSO_4$ and analyzed by gas chromatography.

3.2.4. Analytical procedures

All analyses of reaction mixtures were performed according to the procedures described in Section 2.2.4 (Chapter 2).

3.3. Results and discussion

3.3.1 Using only the micro-mixer of the OSP as reactor

A first trial run was conducted on the OSP in order to determine a base line conversion. This trial experiment was conducted using experimental conditions that would closely resemble the optimum conditions determined for the batch process (cf. Table 2.9). Thus, the trial was conducted at a temperature of 85°C, which represents the "optimum" temperature at which the conventional batch synthesis was performed at. The experiment was conducted at atmospheric pressure, although an increase in pressure (≈ 6 bar) was observed for the streams entering the micro-mixer (Pump 1 in Figure 3.1) which is a common observation brought about by the flow of liquid through the restricted internal structure of the micro-mixer, and which produces a pressure drop across the mixer.

Pump 1 was used to pump the organic phase, and was set at a flow rate of 13mL/min. Pump 2 was used to pump the aqueous phase, and was set at a flow rate of 52mL/min. These settings provided an overall volumetric flow rate of 65 ml/min and fixed the organic to aqueous ratio at one part organic to four parts aqueous, similar to the "optimum" conditions for the batch synthesis of PMD. In this first trial experiment, the delay loops of the OSP were by-passed in order for the results to reflect only the conversion brought on by the micro-mixer itself.

Before describing the results obtained for the first trial experiment, some remarks should be made regarding the selection of the volumetric flow rate of 65mL/min. The reagents which are fed into the OSP plant undergo preheating after which it is combined and mixed within the caterpillar micro-mixer. For optimum mixing inside the micro-mixer, the volumetric flow rate should, according to specification, fall in the approximate range of 4L - 80L per hour (about 67 – 1330mL/min). A flow rate close to the lower limit of this optimum range (4L/h ≈ 65mL/min) was selected for this trial run so as to provide the maximum residence/reaction time. The residence time in the micro-mixer, which is inversely proportional to the flow rate in a continuous, plug-flow reactor, where the density of the reaction mixture can be assumed to remain constant, can be estimated from Equation [3.2] below:

$$t_{res} = \frac{V}{flow\ rate} \qquad [3.2]$$

Since the volume of the micro-mixer is 78μL, the residence time is estimated to be 1.2 milliseconds. (The assumption of constant density is probably correct since the degree of conversion of citronellal into PMD is expected to be very small.)

The continuous contact between the organic and aqueous phase would induce mass transfer and would only occur in the mixing zone of the micro-mixer, after which it exits the plant and the reaction is quenched. Therefore, the reaction time would be only dependent on the volume of the mixing zone/micro-mixer.

The degree of citronellal conversion expected for the trial experiment using the micro-mixer as plug-flow reactor can be estimated from the pseudo first order rate equation as determined for the batch reactor (Chapter 2). The degree of conversion may be defined (with the assumption that the density of the reactor contents remains constant) as Eq. [3.3]:

$$x_C = \frac{[C]_0 - [C]}{[C]_0} \qquad [3.3]$$

By substituting into the first order rate equation:

$$\frac{[C]}{[C]_0} = e^{-k_1 t} \qquad [3.4]$$

the degree of citronellal conversion is found as:

$$x_C = 1 - e^{k_1 t} \qquad [3.5]$$

Thus, for a residence time of 1.2 milliseconds, and a pseudo first order rate constant of 0.2527min^{-1}, the expected degree of citronellal conversion is 5.05 × 10^{-6} (or 0.0005%).

The results obtained for the trial experiment using only the micro-mixer as reactor are summarised in Table 3.5.

Table 3.5: Results for trial on the OSP plant

Run	Temperature (°C)	Combined flow rate (mL/min)	Residence time (milliseconds)	Conversion (%)
1	85	65	1.2	0.1

The results obtained for the trial run showed a conversion (as estimated from GC analysis) of 0.1%, and while it may be argued that this estimation is probably not statistically significant, the GC trace (Figure 3.6) shows clear evidence of some PMD

formation. In view of these results, it was decided to extend the residence time by making use of the OSP's delay loops.

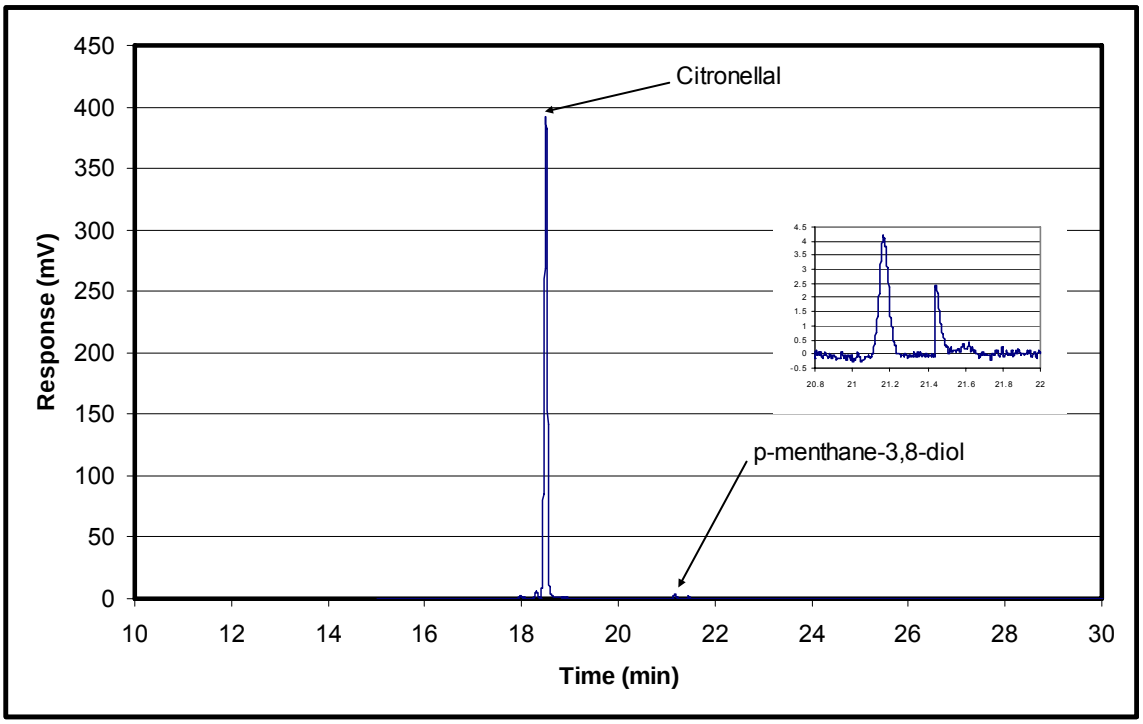


Figure 3.6: GC trace for the OSP micro-mixer experimental run showing presence of PMD

3.3.2. Using the micro-mixer plus delay loops

By directing the reaction mixture as it exited the microreactor through various delay loops (Figure 3.1), one can achieve longer residence times. The delay loops (1 and 2), producing the shortest residence times (used for experimental runs 2 and 3, respectively), are made from 4.1mm (OD) stainless steel tubing, whilst delay loops 3 and 4, producing the longest residence times (used for experimental runs 4 and 5, respectively), are made out of 6.35mm (OD) stainless steel tubing. Table 3.6 summarises the key information for the individual delay loops as well as the estimated residence time for each loop. (Note that for the estimation of residence time the

volume of the micro-mixer as well as the volume of the connecting tube between the micro-mixer and the delay loop has been ignored.) Table 3.7 summarises the results for the conversion obtained for the delay loops and compares the conversions obtained with the estimated expected conversions calculated from the first order rate equation as before.

Table 3.6: Estimated residence times for delay loops

Run	Loop No.	Temp. (°C)	Flow rate (mL/min)	Tube OD diameter (mm)	Tube volume (mL)	Residence time (min)
2	1	85	65	4.1	0.91	0.014
3	2	85	65	4.1	4.55	0.07
4	3	85	65	6.35	18.2	0.28
5	4	85	65	6.35	91.0	1.40

Table 3.7: Comparison of actual versus predicted conversion for OSP's delay loops

Run	Residence time (min)	Estimated conversion (%)	Actual conversion (%)
2	0.014	0.35	0.45
3	0.07	1.75	0.80
4	0.28	6.83	1.36
5	1.4	29.80	2.43

The results obtained (Table 3.7) show that there is a significant difference between the predicted conversion and the observed conversion. The conversion obtained for the delay loops are consistently lower than for the equivalent residence time in the

batch reactor, and this difference becomes higher as the residence time increases (Figure 3.7).

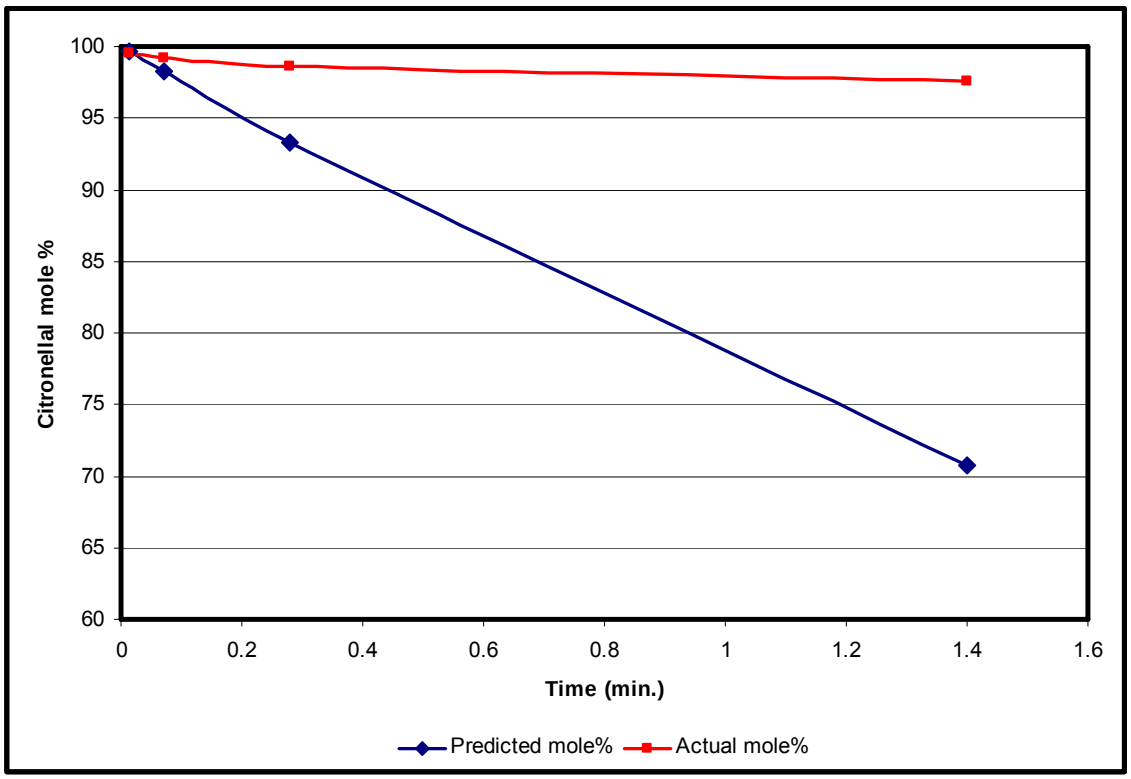


Figure 3.7: Observed and predicted conversions for the disappearance of citronellal using the pseudo first order rate equation

The results obtained clearly imply a mass transfer problem between the aqueous and organic phases in the tubular delay loops, despite advice from the suppliers that flow through the delay loops would remain turbulent and hence provide sufficient dispersion of the organic phase in the aqueous phase. In order to obtain an idea of the type of flow inside the tubes, the Reynolds number for each of the delay loops was calculated ((Eq. [3.6]) (assuming the liquid-phase consisted of only water (Table 3.8).

$$\mathrm{Re} = \frac{\rho VD}{\mu} = \frac{VD}{\nu} = \frac{QD}{\nu A} \qquad [3.6]$$

where:

Re is the Reynolds number

V *is the mean fluid velocity (m/s)*

D *is the diameter of the pipe (m)*

μ *is the dynamic viscosity (Pa.s)*

ν *is the kinematic viscosity (ν = μ/ρ) (m^2/s)*

ρ *is the density of the fluid (kg/m^3)*

Q *is the volumetric flow rate (m^3/s)*

A *is the pipe cross-section area (m^2)*

Table 3.8: Reynolds numbers for delay loops (Flow rate = 65 mL/min and T = 85°C)

Run	Delay loop	Tube diameter (m)	Fluid velocity (m/s)	Density of water at 85°C (kg/m^3)	Dynamic viscosity of water at 85°C (Pa.s)	Reynolds number
2	1	0.001752	0.45	968.508	0.000355	2150
3	2	0.001752	0.45	968.508	0.000355	2150
4	3	0.004572	0.066	968.508	0.000355	824
5	4	0.004572	0.066	968.508	0.000355	824

Generally, for Reynolds number < 2300, laminar flow occurs, while for Re > 2300 turbulent flow occurs.[6] Thus, for the smaller diameter tubes the flow appears marginally turbulent while it is clearly laminar for the larger diameter tubes. The

above calculations are shown only to provide an indication of the type of flow, hence the degree of mixing. For liquid/liquid dispersions, the rate of mass transfer will be determined by the interfacial area between the two phases, i.e. the droplet size of the dispersed phase in the continuous phase. In well-stirred batch reactors, an idea of droplet size may be obtained from the specific energy dissipation from the impeller – the larger the energy dissipation, the smaller the drop size. For tubular columns, the formation of droplets is generally much poorer than for stirred reactors, even in cases where the column contains internal structuring. [7]

For the PMD synthesis, one would want to operate the two-phase system under conditions that would produce a very fine dispersion so as to promote mass transfer between the phases. In order to promote turbulent flow in the empty delay loops, one could alter the following:

- Decrease the pipe diameter; or
- Increase the flow rate.

It is, however, debatable whether any one of these options would be capable of generating a dispersion fine enough to achieve practical mass transfer rates. In addition, reducing the pipe diameter, or increasing the flow rate, would result in impractically long tube lengths.

3.3.3. Packed loops

One way to promote turbulent flow and dispersion of two liquid phases in a tube is to provide the tube with an internal structuring.[7] Delay loops 3 and 4 on the OSP plant, which has the largest internal volume, hence producing the longest residence times, were packed with SiC chips with an average particle size of 0.5mm. In order to estimate the residence times in the packed tubes, it was necessary to estimate the void volume inside the packed tubes. The void volume was determined by filling the respective tubes with water after which the water was blown out with compressed air

into a measuring cylinder. After blowing air through the tube for about ten minutes the volume of water was recorded. The following table shows the volume of water, which represents the void volume inside the packed tubes, obtained for the respective tubes. Table 3.9 lists the void volumes for the packed tubes as well as the estimated residence times for the packed tubes at a volumetric flow rate of 65 mL/min.

Table 3.9: Void volumes and estimated residence times of packed columns

Delay loop	Volume non-packed (mL)	Residence time at 65mL/min (min)	Volume packed (void) (mL)	Residence time at 65mL/min (min)	Void volume % for packed tubes
3	18.2	0.28	10.6	0.16	58%
4	91.0	1.4	38.41	0.59	42%

From the table above, it can be seen that the percentage void volume for the delay loops 3 and 4 differs significantly. This was as the result of the difficulty with which these loops were packed since they were wound. Filling tube 4 was especially difficult as it was 5.6m long, and irregular packing of particles within the loop could have resulted in a low void percentage. Ideally, one would want to fill a straight tube and wound it after it has been filled with silicon carbide. This was not possible at the time.

Table 3.10 shows the actual and calculated conversions for delay loops 3 and 4 at 85°C when they are empty and packed.

Table 3.10: Comparison of conversions in empty and packed delay loops

Delay Loop No.		Citronellal Conversion (%)	
		Calculated	Observed
3	Empty	6.83	1.36
	Packed	4.02	1.36
4	Empty	29.8	2.43
	Packed	13.83	7.45

Despite the difficulty with which the delay loops were packed and the consequent possibility for selective flow through areas where regular packing could not be achieved (as suggested by the measured void volumes), the results clearly indicate the improvement in conversion (relative to a well-stirred batch reactor at the same residence time) when using a packed tube using the same reaction conditions.

3.3.4. Effect of increasing temperature

Despite the fact that the packed delay loops may have been operating in a mass transfer limited domain, it was still of interest to evaluate what the effect of increasing reaction temperature would be on the rate of citronellal conversion. Since it has been shown that the acid-catalysed cyclization of citronellal shows Arrhenius behaviour, the Arrhenius equation (Eq. [3.7]) can be used to estimate rate constants at any temperature.

$$k_1 = Ae^{-\frac{E_a}{RT}} \qquad [3.7]$$

where (from *Chapter 2*): $A = 3.98 \times 10^7 min^{-1}$

$E_a = 56.38 kJ/mol$

$R = 8.3145 J.K^{-1}.mol^{-1}$

Table 3.11 shows some calculated rate constants for temperatures from 85 to 115°C.

Table 3.11: Calculated rate constants for the PMD reaction at various temperatures

Temperature (°C)	k_1 (min^{-1})
85	0.2526
95	0.4218
105	0.6854
115	1.0860

By using the rate constants depicted in Table 3.11 and using the residence times (Table 3.9) for packed delay loops 3 and 4, estimated conversions were calculated (Table 3.12) for the respective temperatures. Experimental runs, equivalent to runs 4 and 5 in Table 3.10, were conducted using packed delay loops 3 and 4, respectively, and during which the reaction temperature for each run was successively increased from 85 to 115°C, whilst maintaining a volumetric flow rate of 65mL/min and using 1:4 organic to aqueous ratio. During these runs, the pressure sensor, which previously measured the pressure before the micro-mixer during the non-pressurized runs, was removed and placed at the exit of the delay loops to ensure that the reaction pressure of the mixture which exited from the delay loops was approximately 10bars. This was to ensure that the aqueous phase remained in the liquid form during reactions >100°C. To achieve these pressures, a needle valve was inserted at the end of the plant to restrict the flow of the reaction mixture, hence increasing the system pressure. The results obtained are summarised in Table 3.12 and illustrated graphically in Figure 3.8.

Table 3.12: Estimated and observed conversions at various temperatures for packed delay loops

Delay Loop No.		3		4	
Residence Time (min.)		0.16		0.59	
k_1	Temp (^oC)	Conversion (%)		Conversion (%)	
		Calculated	Observed	Calculated	Observed
0.2526	85	4.02	1.36	13.83	7.45
0.4218	95	6.63	2.40	22.00	10.50
0.6854	105	10.54	3.76	33.22	16.59
1.0860	115	16.18	5.79	47.26	26.87

The results obtained showed a significant increase in citronellal conversion, as expected from the Arrhenius equation, despite the fact that the delay loops are probably operating in a mass transfer limited domain. These results clearly show that it may be possible to intensify the reaction by increasing the reaction temperature and pressure and that a continuous-flow tubular reactor may very well offer distinct advantages over a traditional well-stirred batch reactor. This can clearly be seen by comparing the conversion achieved at 115^{o}C in delay loop No. 4 (26.87%) to the conversion expected at the "optimum" conditions for a well-stirred batch reactor (operating at 85^{o}C), namely 13.8%. Achieving the rate of mixing (macro-mixing) in a large vessel, even when well-stirred, will become extremely difficult at intensified conditions and result in significant by-product formation.

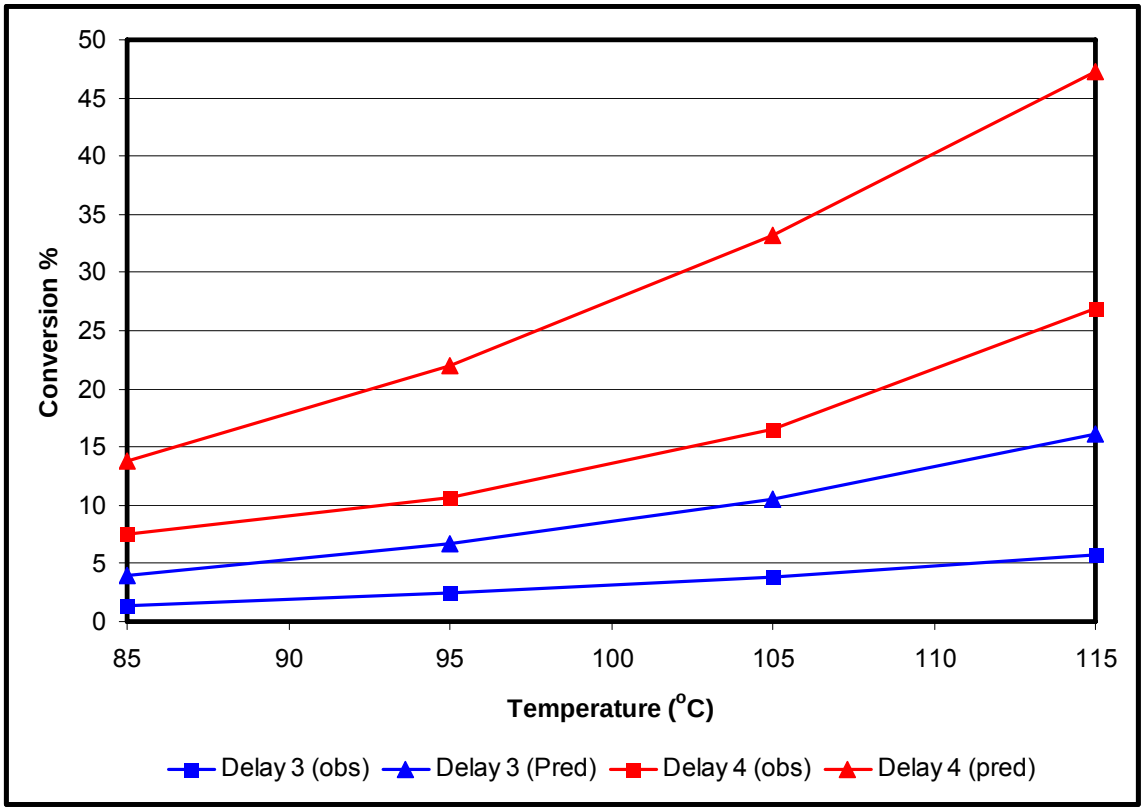


Figure 3.8: Comparison of citronellal conversions for packed delay-loops 3 and 4 at various temperatures

3.3.5. Replacing the caterpillar micro-mixer with a T-piece

Micro-structured reactors generally only started to surface in the late 1980's and are currently still a very specialized area. These reactors are manufactured using highly skilled people and techniques such as advanced micro-laser engineering, lithography and engraving with diamonds. This implies that the cost of this technology is still very high. For example, most of these reactors, despite their high product delivery, still fall in the R100K range for lab-scale equipment, and this does not make it economically viable for small production platforms where units may have to be replicated several times to achieve desired production capacities.

In the present case where use is made of a packed tube as both a reactor and mixing device, the benefit of using the micro-mixer is highly questionable. It was therefore

decided to use a commercially available stainless steel T-piece (which had an internal volume of 189µL and cost about R80 as compared to ~R150k for the caterpillar micro-mixer) for combining the two liquid feed streams. Several reactions were performed over a range of temperatures by using the caterpillar micro-mixer and then repeating these runs with the stainless steel T-piece as an introductory unit. The results obtained are compared graphically in Figure 3.9.

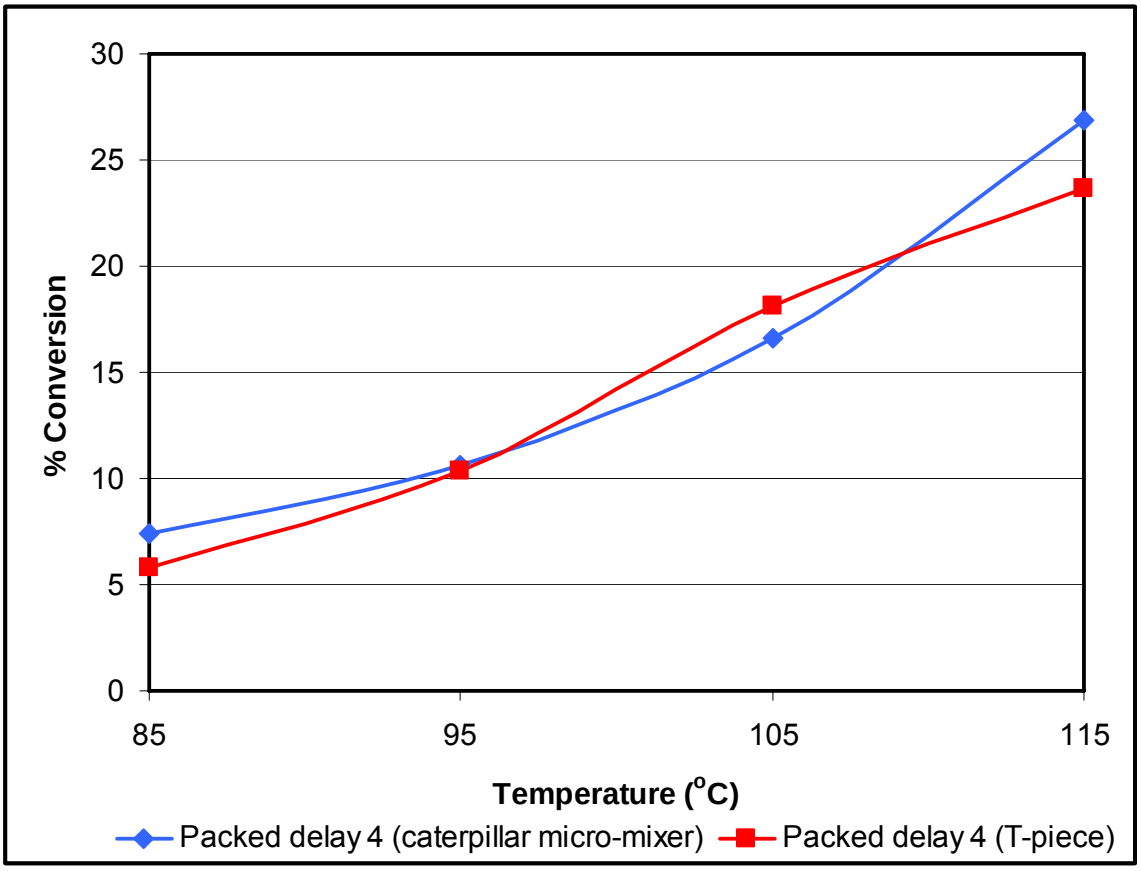


Figure 3.9: Comparison of caterpillar micro-mixer and T-piece configuration

The results above show that little difference was observed between the use of a caterpillar micro-mixer and using an ordinary T-piece configuration. This is generally because the bulk of the mixing occurs as it moves through the packed tube configuration and not during the introductory unit itself.

3.4. Concluding remarks

The results obtained from attempts to perform the cyclization of citronellal on the OSP plant highlighted several issues, including:

- Conventional micro-reactor technology would not be suitable for this particular reaction since the reaction rate, even at elevated temperatures, is too slow to give practical levels of conversions.
- Using open tubes as reactor devices will require either too thin a tube or too long a tube to ensure proper turbulent mixing to be practical.
- Using tubes with an internal packing such as SiC will improve the dispersion of the organic phase into the aqueous phase to such an extent that conversion levels start to approach the conversion levels of a well-stirred batch reactor.
- Operating a packed tube at elevated temperature (and pressure) provides conversion levels far exceeding the conversion levels at the “optimum” well-stirred batch reactor conditions.

Provided that the desired selectivity levels can be achieved for a reactor system comprising packed tubes and operating at high temperature (and pressure), such an approach could be a technically-viable alternative to a well-stirred batch reactor. This possibility is explored in the following Chapter.

3.6. References

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Chapter 4

Synthesis of p-menthane-3,8-diol on a small production platform

Abstract

A continuous-flow, tubular reactor system was designed and constructed for the synthesis of p-menthane-3,8-diol. Advanced statistical techniques were used to investigate the effect of variables such as temperature, acid concentration, reactor length, flow rate and the organic to aqueous ratio on the selectivity and on the reaction. Mathematical models were derived for citronellal conversion, yield of PMD and yield of PMD-acetals, and used to predict the concentrations of citronellal, PMD and PMD-acetals at set experimental conditions. The results obtained showed that it was possible to obtain a product which approached desired specifications. Observation of a brown precipitate during sampling when neutralization of the acid phase was done showed that corrosion of the inner pipe walls were occurring at temperatures >130°C. The formation of Fe^{2+} during the continuous process possibly acts as a Lewis acid catalyst that catalyzes both the PMD and PMD-acetal formation reactions. The results highlighted the importance of material of construction for continuous-flow production systems.

Keywords: PMD, SPP (small production platform)

4.1 Introduction

While it is generally recognized that well-stirred batch reactors are best suited for performing reactions involving liquid-liquid dispersions.[1] There are a number of motivating factors for evaluating continuous-flow, tubular reactor technology more closely for the potential commercial production of PMD. These factors include:

- The results of the scale-up studies for the batch process (Chapter 2) have shown that it would be quite difficult to limit the extent of formation of PMD-acetal by-products in a large volume batch reactor.
- The formation of PMD-acetals consumes two moles of starting material for every mole of PMD-acetal formed, hence affects the process economics substantially. In addition, the presence of PMD-acetals in the final formulated (insect repellent) product affects the performance of the repellent product strongly, hence the requirement to restrict the PMD-acetal concentration in the repellent-grade PMD to <1.0%.
- The removal of PMD-acetals from technical-grade PMD is not a straight forward process (to be discussed in the following chapter).
- The capital cost associated with a large batch plant, especially involving pressure equipment for allowing reactions to be performed under pressure, would be prohibitively expensive, especially for a small production company. In addition, sizing of such a batch plant would be extremely difficult given the uncertainties associated with the nature of the proposed business (new insect repellent). Once such a batch facility has been constructed, future production capacity is essentially fixed and allows very little flexibility should market demand change (up or down).

The results described in the preceding chapter, where the commercial OSP was used to evaluate the potential of performing the PMD synthesis in a continuous-flow tubular reactor, have provided sufficient evidence to warrant further investigation of such a

process. It was, therefore, decided to construct a purpose-built tubular reactor comprising packed tubes to fully evaluate the synthesis of PMD. This allowed two essential hypotheses to be evaluated, namely:

- That by intensifying the synthesis of PMD, the kinetics of desired product formation reactions could be enhanced selectively, at least up to a point, to allow increased selectivity towards PMD at reduced levels of PMD-acetal formation; and
- That by accurately controlling the level of conversion of citronellal in a continuous-flow tubular reactor, the level of PMD-acetal formation can be restricted to a level where its specific removal from the technical grade PMD would no longer be required.

Apart from the testing of the two hypotheses stated above, the construction and evaluation of the tubular reactor system would also allow evaluation of the potential commercial production of PMD in a production facility comprising a number of tubular units where “scale-up” can be achieved through a process of “numbering up” of the basic tubular design. If viable, such an approach would overcome the requirement of a heavy initial capital investment to construct a batch plant while the business is still very small, and at the same time it will remove the restriction on future production capacity as the basic production system can be replicated as and if the demand for the product increases. In the remainder of this thesis, the concept reactor design is referred to as a “Small Production Platform” (SPP), since its basic footprint is “small” (less than 1 m^2), and its design principle provides the “platform” for increased production capacity by numbering up the basic reactor concept.

4.2 Experimental

4.2.1. Design and construction of SPP rig

Diagram 4.1 shows the schematic representation of the test rig designed and constructed for the evaluation of the production of PMD in a continuous-flow, packed tubular reactor system.

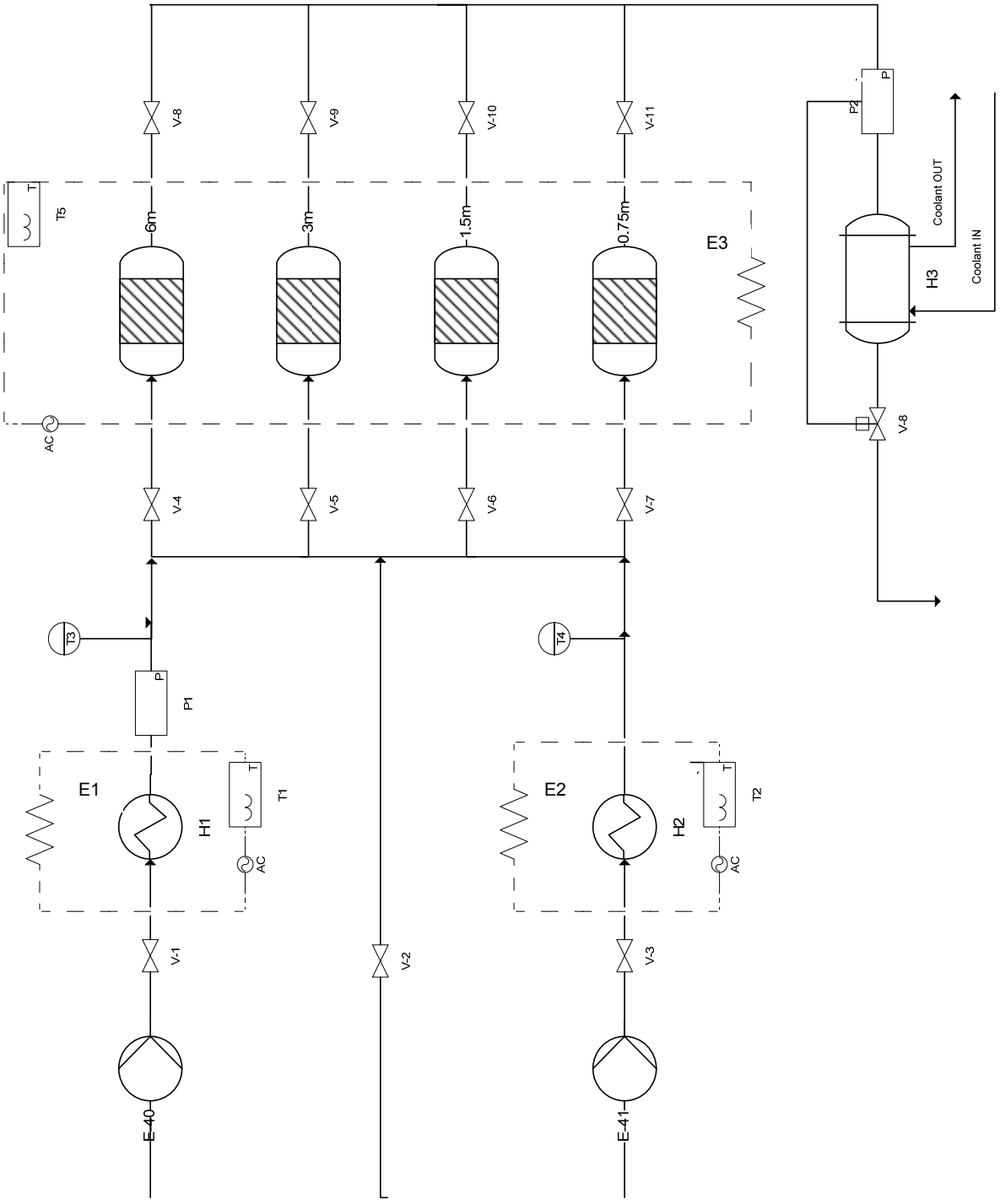


Diagram 4.1: Schematic representation of SPP test rig

As first step to the construction of the SPP, a box frame was constructed from mild steel square tubing which would house the parts for the reactor system shown in Diagram 4.1. The frame size was 500x1000x400mm. A stainless steel plate

(500x1000x2mm) with holes drilled into predetermined positions was connected to this frame with steel hinges. The addition of the hinges allowed one to lift up the plant at any moment to inspect or replace desired parts. The diagram below shows the box frame and stainless steel plate.

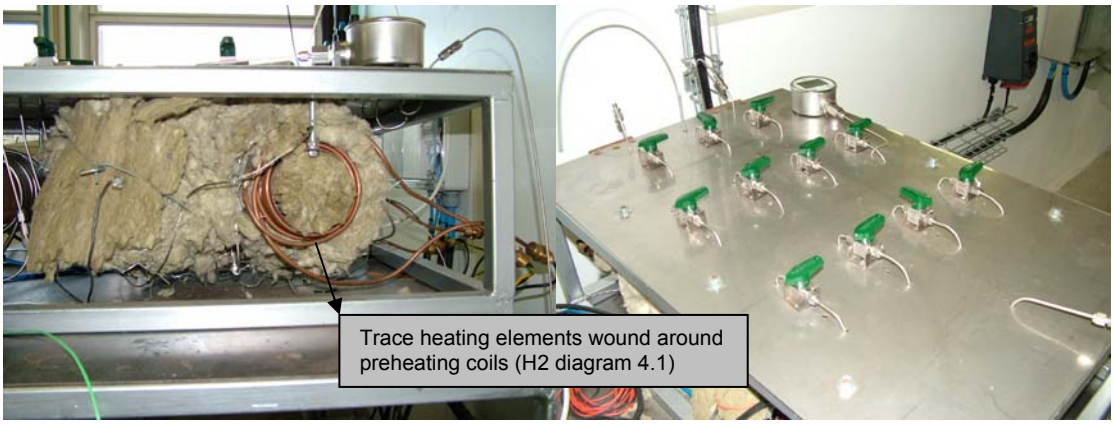


Figure 4.1: Side and top view of the SPP test rig reactor

Three mild steel pipes of 10cm in diameter and 45cm long were suspended from the stainless steel plate via 12mm (OD) threaded galvanised rods. These steel pipes formed the support for heat exchangers H1, H2 and H3 and also for the individual tubular reactors. The side of the steel pipe is shown in Figure 4.1.

During the design of the new reactor, it was decided to address constraints such as the use of an oil bath to heat the respective components of the plant by rather using electrically heated elements to heat up respective components of the SPP test rig. The cross-flow heat exchangers in Figure 3.1 were replaced by preheating coils H1 and H2 in Diagram 4.1. These coils were surrounded by 1000W stainless steel trace heating elements (E1 & E2) which could heat the reagents to temperatures up to 200°C. The temperatures of these preheating coils could be set independently to allow for the necessary heat transfer required at certain flow rates. Conversely, the continuous flow of liquid through these preheating coils acted as heat sinks when the

reagent streams needed to be cooled down quickly. In this way, reactions could be performed at a variety of temperatures without causing long delays during operation or adjustment of the experimental sequence.

All of the temperature controls, reaction pressure and reaction stream temperatures could be set and monitored by a central control box which was constructed and linked to the SPP test rig reactor. The control box is shown below.

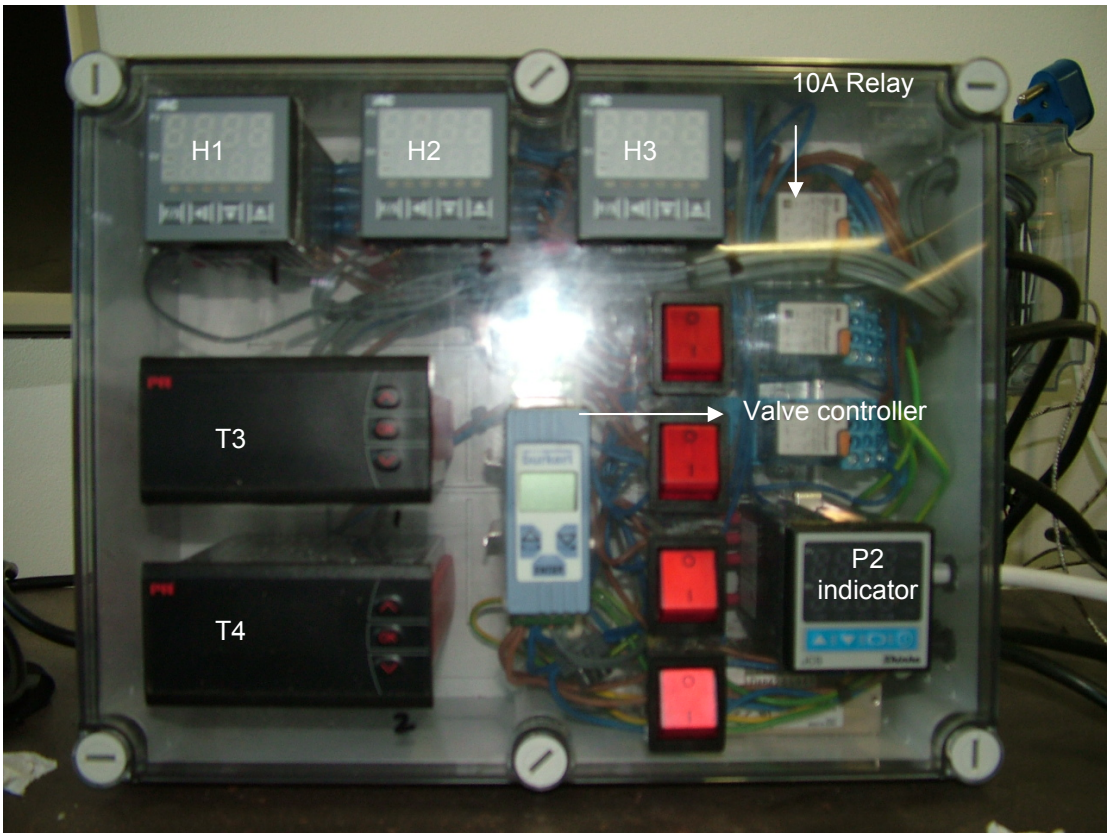


Figure 4.2: Temperature set/indicator and pressure control unit of the SPP test rig

The control box was constructed from a commercially available PVC box with a transparent cover which allowed one to see the electrical components within it. Holes were made in the cover through which various PID controls and display unit were inserted. The connections related to the electric wiring of the respective components are shown in Diagrams 4.2 and 4.3.

The following diagrams show the electrical connections for E1, E2 ,E3 and the electronic valve control system.

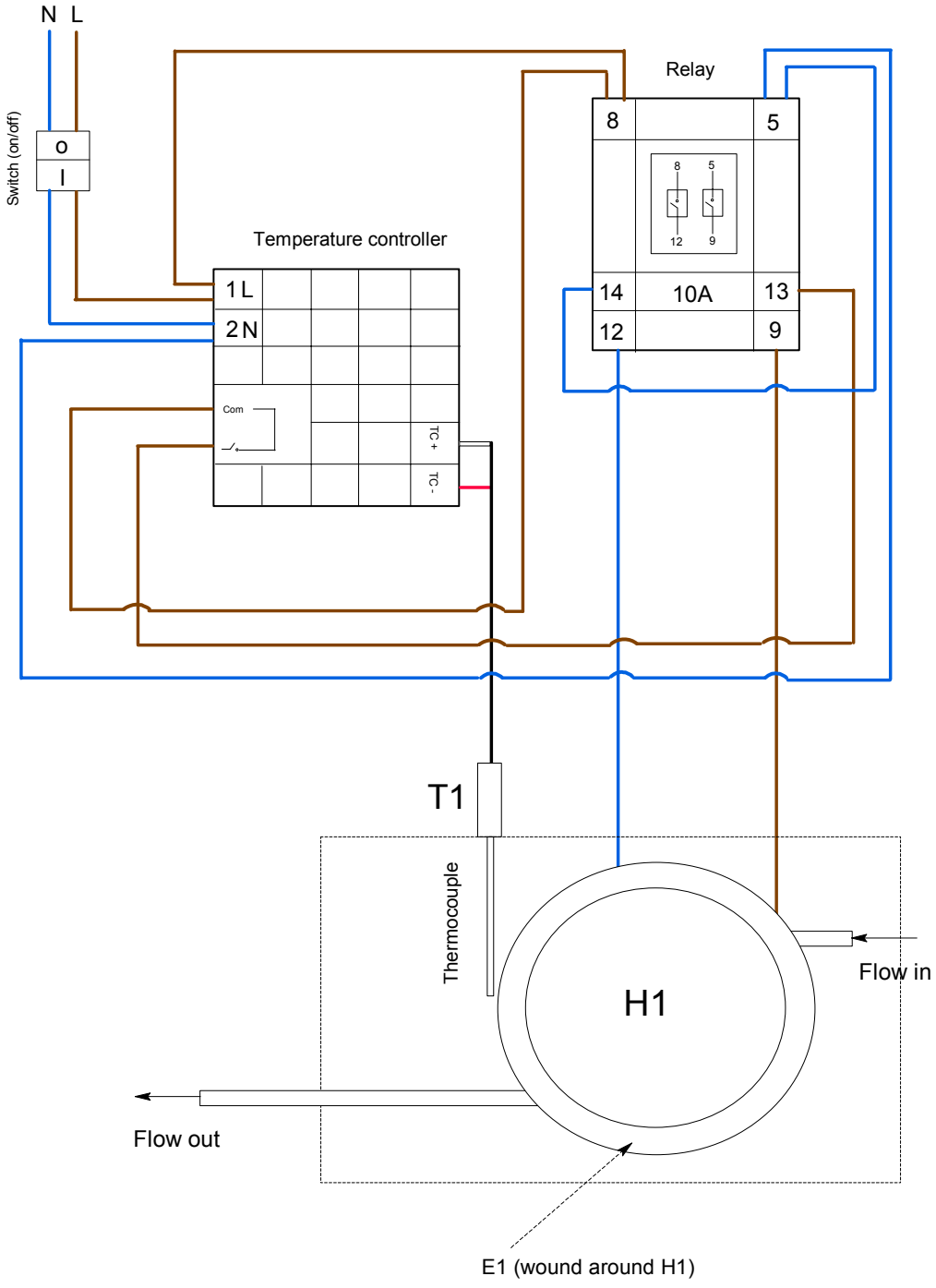


Diagram 4.2: Electrical diagram for E1 (similar connections for E2 and E3) diagram 4.1

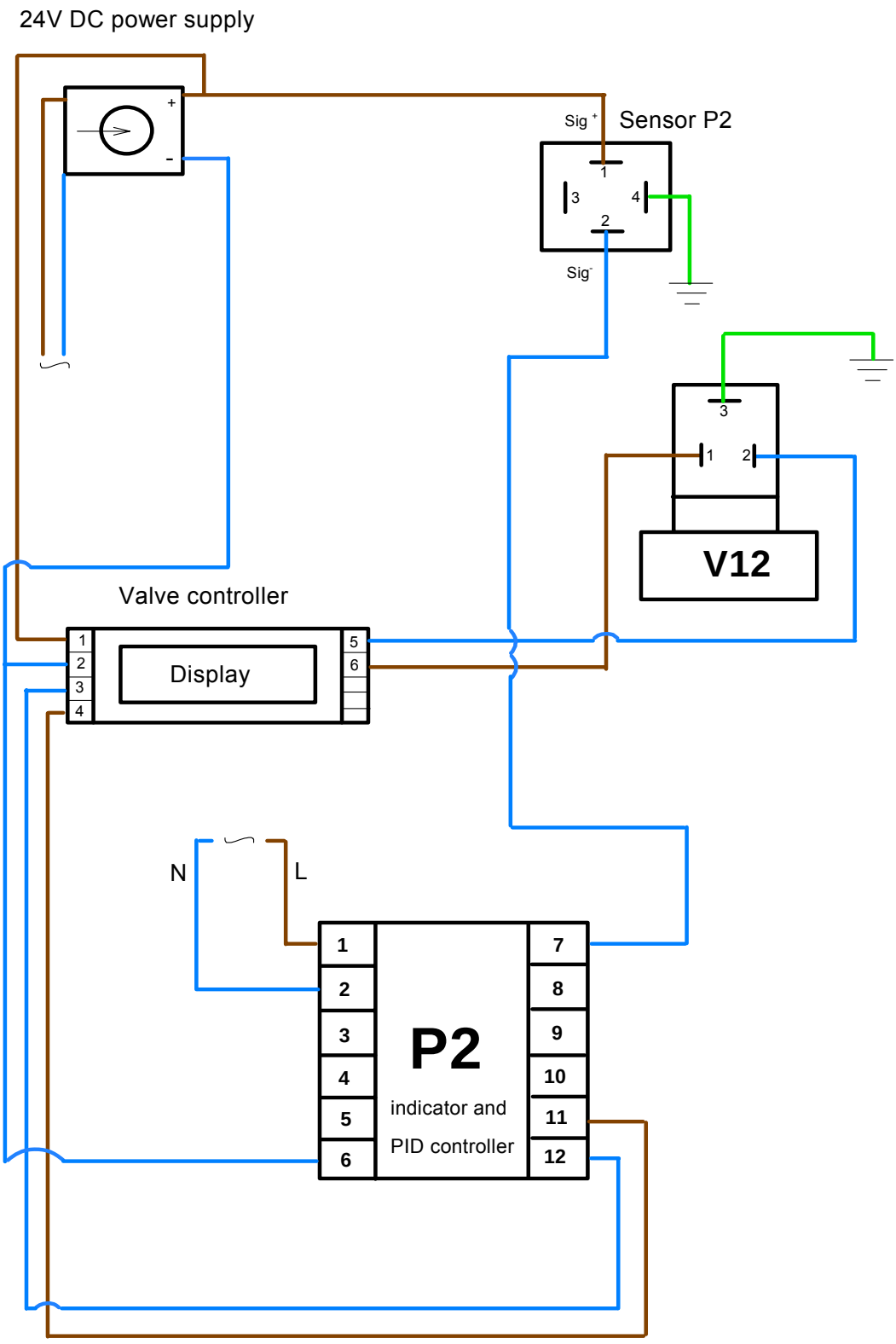


Diagram 4.3: Electrical diagram for electronic pressure valve P2 and V9 in Diagram 4.1

Instead of using the caterpillar micro-mixer, a standard 1/8” T-piece was used to introduce the reagent streams into packed delay loops of different sizes which formed the main reaction zone. The replacement of the micro-reactor had previously shown to have little influence on the conversions (Chapter 3). The reaction stream could be directed through any of these respective tubular reactors at any time without stopping the process when different reaction times were required. These packed delay loops were in turn coiled around a cylindrical pipe which contained a heating element (E3) which helped to maintain the set reaction temperatures.

The reaction zone was followed by a tube-in-tube heat exchanger (H3) similar to the one that was used on the OSP. However, the length of the heat-exchanger was changed from approximately 0.5m to 6m in order to ensure that the product stream was cooled down properly even at flow rates higher than 60L/h. Water from a cooling tower at 18°C and a pressure of 4 bars was fed into the outer shell of the heat exchanger in a countercurrent way to the reaction stream to allow for maximum efficiency. The heat exchanger is now shown below:

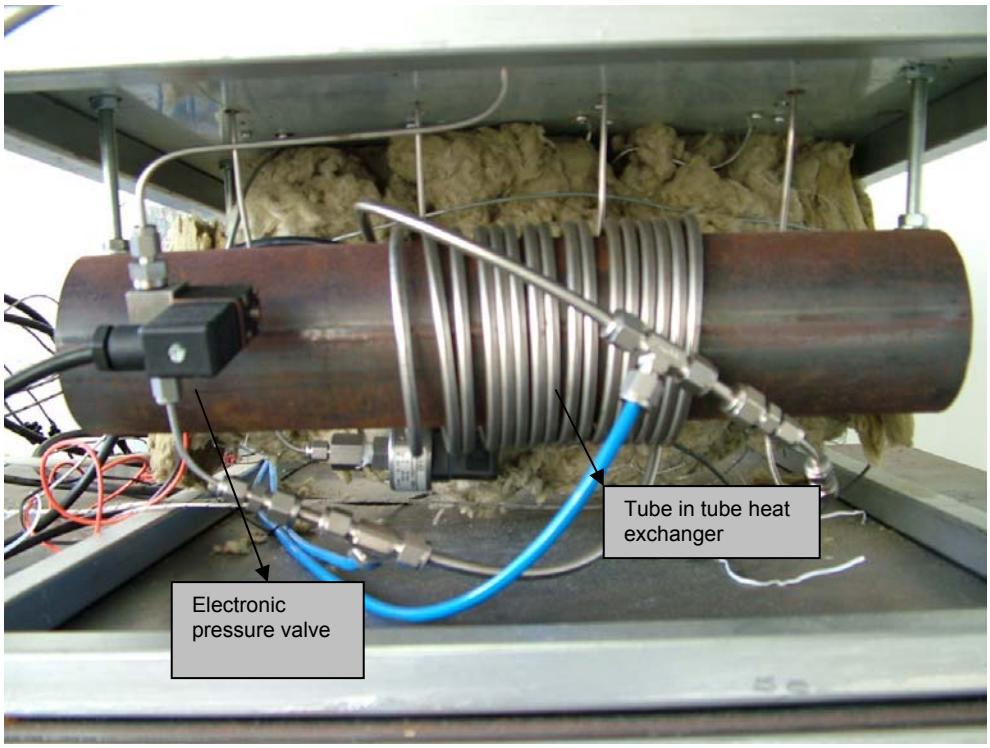


Figure 4.3: Electronic pressure valve and tubular heat exchanger of the SPP test rig

The pressure of the system was controlled by an electronic valve which enabled one to set the reaction pressure and also observe the pressure after the reactor zone (Figure 4.3). Pressures before the reactor zone (back pressure) were measured by a pressure sensor capable of measuring pressures up to 100bars.

The parts used to construct the SPP were sourced from various suppliers. The following table shows the parts that were used, the quantities, relevant supplier and prices thereof.

Table 4.1: The parts and their relevant prices used for the SPP test rig are listed in

Part	Part no.	Supplier	Quantity	Price (2007) each (R)
$^1/_8$" Union tee	SS-200-3	Swagelok	13	152.08
$^1/_8$" Union	SS-200-6	Swagelok	4	69.09
$^1/_8$" Seamless Tubing (6m)	SS-T2-S-028-6ME	Swagelok	2	60.99p/meter
$^1/_8$" Ferrule set	SS-200-SET	Swagelok	10	14.32
¼" Union tee	SS-400-3	Swagelok	3	
¼" Seamless tubing (6m)	SS-T4-S-035-6ME	Swagelok	5	43.64p/meter
¼" to $^1/_8$" Reducing union	SS-400-6-2	Swagelok	14	72.13
¼" to $^1/_8$" Reducing union (bored through)	SS-400-6-2BT	Swagelok	2	83.08
¼" Ferrule set	SS-400-SET	Swagelok	10	11.80
Valves V1-V11	SS-2P4T	Swagelok	11	563.00
Female connector	SS-200-7-4	Swagelo	1	84.00
Male connectors	SS-400-1-2RS	Swagelo	2	71.60
1000W trace heating elements (H1 and H2)	N/A	Industrial thermal	2	2596.5
Thermocouples T1, T2 and T5 (1.5x100mm)	JY0152C2	Industrial thermal	2	145.65
PID controllers	ANC ND545	Industrial thermal	3	635.00
500W element (H3)	N/A	Industrial thermal	1	78.00
Digital Pressure gauge P1 (0-100bar)	DG-10	Wika	1	2490.00
Temperature displays for T3 and T4	PR5714	Wika	2	872.5

Table 4.1 continued on next page….

Table 4.1 continued				
Part	**Part no.**	**Supplier**	**Quantity**	**Price each (R)**
Electronic back pressure regulator (0-12bar), PID controller and pressure transmitter (1/8" connectors)	Bürkert 2824	Wika	1	5875
Relay	Type 55-32	Cosmotronics	3	123.99
Relay base	-	Cosmotronics	3	87.69
PVC BOX	SL0878L00	Cosmotronics	1	275.00
Silicon Wire (red)	**-**	Cosmotronics	3	4.20
Silicon Wire (black)	**-**	Cosmotronics	3	4.20
Din Rail	**-**	Cosmotronics	1	26.32
10/16A Rocker switch	**-**	Cosmotronics	3	157.92
1x3 Core white c/Tyre p.m.	**-**	Cosmotronics	6	53.00
Grommets	**-**	Cosmotronics	10	10.50
DC power supply		Postma-Postma	1	285.00

Before insulation of the SPP-rig components was done, the plant was pressure tested by flowing water at a total flow rate of 40mL/min whilst slowly increasing the system pressure at P2 via the electronic pressure valve to 10 bars. The reactor was run at these settings for 10min and inspected for leaks. Calibration of the temperature controller was not necessary as the types of controls used in the control box contained internal calibration systems.

4.2.2. Experimental procedure for the operation of the SPP test rig

The SPP test rig was switched on and the relevant valves were opened. The cooling tower utility at the InnoVenton kilo-laboratory was switched on and the valve feeding the cooling water to the SPP test rig opened. The SPP test rig preheating coils H1

and H2 were set to 70°C and E3 to the desired reaction temperature. The two HPLC pumps were started and allowed water to pump through the plant at 20mL/min (per pump) as a preliminary flushing step. The water streams were changed to the respective organic and aqueous phases, the flow rate stepped up/down to the desired flow rate and preheating coils E1 and E2 gradually increased to the desired reaction temperature. The electronic valve at the end of the plant was adjusted until a backpressure reading of 6 bars was observed. This was to ensure that the aqueous phase maintained a liquid state during the various reactions that were performed at temperatures >100°C.

After pressure and temperature stabilization was observed on the control unit of the SPP test rig (±15min), a suitable amount of reaction mixture exiting the SPP test rig was sampled directly into 100mL of a 2.5% sodium bicarbonate solution (room temperature). This was done to neutralize the catalyst and quench the reaction. Thereafter the organic phase was separated and washed three times with hot (80°C) DI water, each time discarding the aqueous layer and retaining the organic layer. The organic layer was then dried (using anhydrous $MgSO_4$) and analyzed by gas chromatography.

4.2.3. Materials

All the materials that were used for the synthesis of PMD, the sources of procurement and the respective grades, are listed in Table 4.2, while the solvents used for analytical purposes are listed in Table 4.3. All materials were used as received unless otherwise specified.

Table 4.2: Reagents for synthesis

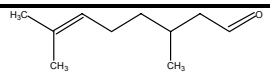
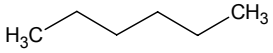
Name	Structure	MM g/mol	Supplier	Grade Purity
Citronellal		154.14	Merck	AR
Sulphuric acid	H_2SO_4	98.08	Merck	95-98%
Sodium bicarbonate	$NaHCO_3$	84.01	Saarchem	AR

Table 4.3: Reagents for analysis

Name	Structure	MM g/mol	Supplier	Grade Purity
n-Hexane		86.1766	Merck	AR
Heptane	isomers	100.21	Merck	AR

4.2.4. Analytical procedures

All analyses of reaction mixtures were performed according to the procedures described in Section 2.2.4 (Chapter 2).

4.2.5. Statistical procedures (design and analysis of experiments)

The statistical analyses were done using multiple linear least squares regression using the STATISTICA V.5 software package.

4.3. Results and discussion

4.3.1. SPP test rig design

The results obtained and the observations that were made during trial experiments performed on the OSP provided the basis for the design of the SPP test rig. Several aspects of the OSP design were identified as being problematic and which needed modification. These include:

- The ability to "plug and play", i.e., removal and reconfiguration of components to allow specific reactions to be performed.
- The ability to rapidly and conveniently change between operating temperatures. The latter proved to be extremely inconvenient during operation of the OSP since heat transfer relied on the principle that the operating components of the plant was immersed in hot oil. Not only did the oil bath take up to 24 hours to cool down to ambient temperature, but it also left the parts greasy and created a difficult environment to work in. The inability of the oil to cool down easily also made it extremely difficult to rapidly change between set points with a difference greater than 10°C, especially if the new set point was below the current set point. For this reason, most reactions performed on the OSP had to be arranged with regards to their temperatures in increasing order to save time during operations. To overcome these shortcomings, an electrical heating system was used on the SPP test rig in place of an oil heat exchange system (see Section 4.2.1 for details).
- The cross-flow heat exchangers of the OSP. These are used to heat up the two independent reagent streams before entering the reaction zone and they provide two main problems. First, in order to perform reactions above 100°C, oil had to be used as heat exchange medium which was not only difficult to work with, but the higher viscosity of the oil restricted its flow through the heat exchangers to produce enough heat transfer. Secondly, the temperature of, and the rate of oil entering and leaving the respective cross flow heat exchangers were the same for each exchanger without the

option of adjusting either. On the SPP rig the two reagent streams were passed through preheating coils (Section 4.2.1) which were independently heated by electrical heaters.

- The delay loops on the OSP. These varied in diameter which meant that linear velocities changed when interchanging between tubes of different internal diameters even when working at the same volumetric flow rates. Furthermore, the tube lengths were fixed and no facility existed to interconnect two or more of the tubes to provide for a wider variety of tube lengths. This meant that reactor residence time, determined by tube length, could not be studied independently from flow rate. On the SPP rig, all reactor tubes were of the same internal diameter, and tubes of different lengths were used that could be interconnected to give a wider choice of reactor lengths. This provided some variable residence time capability on the SPP rig so that the influence of flow rate could be evaluated independently from the reactor residence time.

4.3.2. Experimental design

In any experiment, be it synthetic or analytical, there are a number of factors or variables that may have an effect on the outcome of the experiment. In order to understand the effect of these factors on the response variables and the interactions between them, careful experimental planning is required. Classical determination of the effects of such variables usually involves varying only one variable and keeping the remaining variables constant. This however, could obscure the real effect of such a variable as it might be interacting with other variables. This phenomenon is especially common in the region of optima (or minima) which makes finding an optimum set of conditions for a synthetic (or other) procedure very difficult using the traditional vary one-factor-at-a-time approach. Experimental designs prove to be very useful tools in this particular area as they allow us to investigate the influences of each individual variable and also the various interactions between them.

Before considering the use of these designs, it is important to understand and define the response variables to be studied. In this particular instance, it is known that the purity of the PMD, which was defined earlier, is very important. It was already stated in Chapter 1 that it would be desirable to obtain a product which contains at least 99.0% PMD, and less than 1.0% PMD-acetals. One can use a great deal of the knowledge already gained from the batch studies and OSP trial runs to help identify the variables that are important to obtain a product with such a composition.

From this prior knowledge, it is evident that the factors that influence the acid-catalyzed reaction of citronellal are:

- Temperature;
- Acid concentration;
- Organic to aqueous ratio; and
- Reaction time.

In a tubular reactor, the reaction time is determined by the flow rate and the tube volume, or the void volume in the case of a packed tube (Eq. [4.1]).[2]

$$Time = \frac{V}{F} \qquad [4.1]$$

where: V = volume (mL)

F = Flow rate ($mL.min^{-1}$)

Therefore, to vary the reaction time either of the reactor volume (tube length or diameter) or the volumetric flow rate can be changed. Any one of these changes will impact upon the linear velocity of the fluid flow (Eq. [4.2]). Since fluid elements move chaotically between the particles and cause mixing of the fluid elements due to turbulence and molecular diffusion[3] (see Figure 4.4), a change in linear fluid velocity may change the rate of mass transfer and, hence, the reaction kinetics.

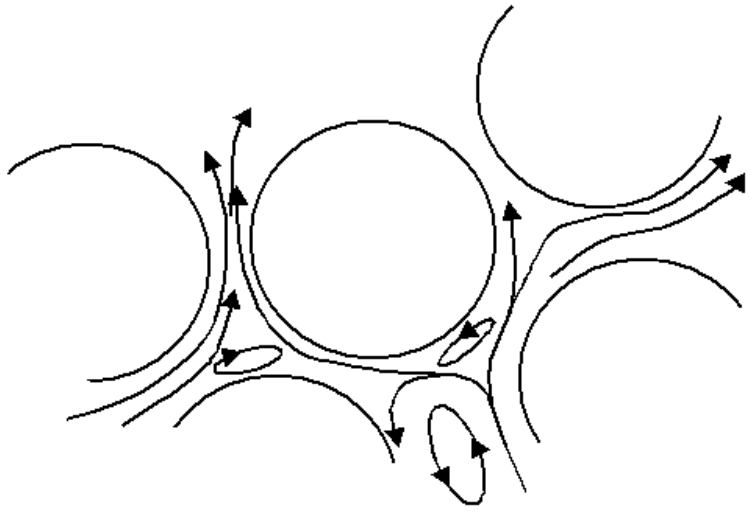


Figure 4.4: Chaotic movement of fluid through a packed tubular reactor

$$Fluid\ velocity = \frac{F}{\pi r^2} \qquad [4.2]$$

The fluid velocity can be obtained by dividing the reactor length (L) by the residence time (T):

$$Fluid\ velocity = \frac{L}{T} \qquad [4.3]$$

Since the flow rate (F) is given by $F = \frac{V}{T}$, where V is the volume of the reactor pipe, and by using the fact that $V = \pi r^2 L$, it can be shown by algebraic substitution that:

$$Fluid\ velocity = \frac{F}{(\pi r)^2} \qquad [4.4]$$

This functional relationship is only valid when the reactor pipe radius r is the same for the total reactor pipe length.

In the case of the SPP rig, all the reactor pipe diameters are the same, with the result that residence time can only be varied by either changing the tube length, or changing the volumetric flow rate. For the design described in this work, it was decided to

include both parameters as independent variables so as to be able to evaluate selectivity to the products/by-products of interest as a function of flow rate (degree of mixing or mass transfer) and residence time (tube length) independently.

Based on the results obtained on the OSP (Chapter 3), reaction temperatures were selected which would significantly speed up the kinetics of the reaction to give good conversions in a short period of time (above 20% in ≈1 minute). The SPP rig constructed allows for reaction temperatures from ambient up to 180°C. Therefore it was decided to select a temperature range which falls between 100 and 150°C.

As the acid-catalyzed cyclization of citronellal is affected by mass transfer, changing the ratio of the organic to the aqueous medium can influence the interfacial surface area between the phases, thereby influencing mass transfer. Since the rate of mass transfer would affect the conversion rate and selectivity of the reaction, the ratio of organic:aqueous phase should be included in the selection of variables to investigate. Since the two phases will be pumped into the reactor by two individual pumps, the flow rate for each pump and the respective ratios were taken into account. The flow rates for each pump were calculated as follows.

$$Flow\ rate_1 = Total\ \ flow\ rate * Ratio \qquad [4.5]$$

$$Flow\ rate_2 = Total\ \ flow\ rate - Flow\ rate_1 \qquad [4.6]$$

The total flow rate was chosen according to the pumps and backpressures that the SPP test rig could tolerate. A preliminary test on the plant showed that a back pressure of about 45 bars was obtained at a flow rate 65mL/min using the 6m tube with an approximate void volume of 50% when packed with SiC particles having an average particle size of 0.5mm.

The reaction variables, their actual settings used during each experimental run, as well as the experimental responses measured, are shown in Table 4.4.

Table 4.4: Design and responses for the modelling of the SPP rig

Run No.	Length (m)	Acid (%v/v)	Flowrate (mL/min)	Ratio (V Org/ Tot V)	Temp (^{o}C)	Conversion (%)	PMD (mol %)	Acetal (mol %)
1	6.00	0.16	45.00	0.31	110.50	11.21	16.72	0.23
2	6.00	0.08	33.00	0.24	120.30	15.43	19.04	0.21
3	6.00	0.08	33.00	0.42	119.85	8.01	20.46	0.11
4	6.00	0.23	33.00	0.24	120.40	29.31	23.05	0.08
5	6.00	0.23	33.00	0.42	120.38	14.30	23.04	0.12
6	6.00	0.08	57.00	0.23	120.47	10.20	14.67	0.06
7	6.00	0.08	57.00	0.40	120.22	7.33	7.54	0.03
8	6.00	0.23	57.00	0.23	120.18	31.56	27.59	0.39
9	6.00	0.23	57.00	0.40	120.42	16.76	13.74	0.08
10	6.00	0.16	21.00	0.33	130.40	20.20	32.88	0.21
11	6.00	0.00	45.00	0.31	130.25	2.35	21.11	0.07
12	6.00	0.16	45.00	0.13	130.35	52.10	45.61	1.93
13	6.00	0.16	45.00	0.31	130.08	29.23	32.71	0.52
14	6.00	0.16	45.00	0.31	130.06	29.58	10.74	0.13
15	6.00	0.16	45.00	0.31	130.19	27.84	1.79	0.17
16	6.00	0.16	45.00	0.31	130.41	28.31	49.89	0.80
17	6.00	0.16	45.00	0.31	130.64	28.43	28.11	0.21
18	6.00	0.16	45.00	0.31	130.19	27.98	28.52	0.20
19	6.00	0.16	45.00	0.51	130.30	16.06	26.85	0.21
20	6.00	0.31	45.00	0.31	130.49	36.51	27.38	0.17
21	6.00	0.16	69.00	0.32	130.32	25.54	26.99	0.65
22	6.00	0.08	33.00	0.24	140.26	34.41	27.08	0.14
23	6.00	0.08	33.00	0.42	140.32	21.95	15.43	0.12
24	6.00	0.23	33.00	0.24	140.32	50.99	34.94	0.55
25	6.00	0.23	33.00	0.42	140.34	34.58	44.59	1.59
26	6.00	0.08	57.00	0.23	140.15	39.20	25.24	0.12
27	6.00	0.08	57.00	0.40	140.26	23.19	9.78	0.02
28	6.00	0.23	57.00	0.23	140.38	53.63	6.87	0.03
29	6.00	0.23	57.00	0.40	140.10	40.35	30.45	0.37
30	6.00	0.16	45.00	0.31	150.01	53.08	16.20	0.08
31	10.50	0.16	80.00	0.31	130.18	50.10	36.59	0.86
32	10.50	0.16	80.00	0.31	130.18	50.51	22.36	0.09
33	10.50	0.16	70.00	0.31	130.18	49.48	49.71	1.60
34	10.50	0.16	70.00	0.31	130.18	48.63	38.01	0.79
35	10.50	0.16	60.00	0.31	130.18	52.54	24.82	0.10
36	10.50	0.16	60.00	0.31	130.18	51.21	30.91	0.35

Table 4.4 continued								
Run No.	**Length (m)**	**Acid (%v/v)**	**Flowrate (mL/min)**	**Ratio (V Org/ Tot V)**	**Temp (^{o}C)**	**Conversion (%)**	**PMD (mol %)**	**Acetal (mol %)**
37	10.50	0.16	50.00	0.31	130.18	48.36	25.60	0.24
38	10.50	0.16	40.00	0.31	130.18	45.68	25.52	0.15
39	10.50	0.16	30.00	0.31	130.18	42.54	29.66	0.13
40	9.00	0.16	59.00	0.31	130.18	39.27	30.57	0.15
41	9.00	0.16	50.20	0.31	130.18	38.40	31.93	0.18
42	9.00	0.16	41.20	0.31	130.18	37.87	34.76	0.25
43	9.00	0.16	36.00	0.31	130.18	38.41	34.40	0.22
44	9.00	0.16	32.40	0.31	130.18	35.14	34.84	0.17
45	9.00	0.16	29.60	0.31	130.18	34.02	34.91	0.14
46	9.00	0.16	27.30	0.31	130.18	33.01	38.61	0.28
47	6.00	0.16	80.00	0.31	130.18	34.93	41.18	0.31
48	6.00	0.16	80.00	0.31	130.18	29.13	43.73	0.41
49	6.00	0.16	80.00	0.31	130.18	28.69	47.24	0.44
50	6.00	0.16	46.00	0.31	130.18	28.75	46.17	0.36
51	6.00	0.16	32.00	0.31	130.18	23.56	44.90	0.41
52	6.00	0.16	32.00	0.31	130.18	26.31	43.53	0.30
53	6.00	0.16	25.00	0.31	130.18	24.04	45.38	0.35
54	6.00	0.16	20.00	0.31	130.18	20.18	45.75	0.32

The acid solutions used during the design experiments were made up in 25L polypropylene drums, and the actual concentrations determined by titrating against a standard NaOH solution to make sure that the concentrations were correct. Table 4.5 shows the results for the titrations.

Table 4.5: Actual initial acid concentrations used in the design experiments

% H_2SO_4 (v/v)	
Setting	**Actual**
0.005	0.0048
0.08	0.0801
0.155	0.1559
0.23	0.2319
0.305	0.3090

Before discussing the results obtained from the design experiments, a few remarks should be made regarding the design used. The design comprises a full central composite design in which the levels for the variables temperature, acid concentration, organic to aqueous ratio, and flow rate, were varied over five levels. This allowed the determination of a full experimental response surface of the variation in the experimental response as a function of these variables. In addition, the replication of five experimental runs at the centre of this central composite design allowed an estimation of the magnitude of the experimental variation in all the responses that were measured.

To the above central composite design experiments were added additional experiments for three different tube lengths, namely 6m, 9m, and 10.5m. These additional experiments were carried out using the experimental settings for acid concentration, temperature and organic to aqueous ratio used at the centre of the central composite design, and varying only the volumetric flow rate. This allowed the estimation of the effects of residence time independently from flow rate (so as to be able to observe the effect of mass transfer). Tube lengths shorter than six metres were not considered during this design so as to ensure a reasonable degree of citronellal conversion, and hence to be able to obtain a reliable evaluation of the selectivity trends at reasonable (practical) conversion levels.

Response surface models (polynomial equations) were determined for each one of the experimental responses, namely conversion, PMD yield and PMD-acetal yield, by multiple Least Squares regression using the Statistica V5 Software package[*]. Each one of the models are discussed individually in the section to follow.

[*] With special thanks to Mr C Bosma of InnoVenton who assisted with the mathematical modelling and statistical analysis.

4.3.2.1. Conversion

By using data provided in Table 4.3 and using stepwise regression, the best fitting model which describes the conversion of citronellal is given by:

$$\hat{Y} = b_0 + b_1 L + b_2 L^2 + b_3 A + b_4 A^2 + b_5 F + b_6 F^2 + b_7 R + b_8 R^2 + b_9 T + b_{10} T^2 + b_{11} FL \quad [4.7]$$

In the above model:

$\hat{Y}$ = Estimated citronellal conversion;
b_0 = the intercept (or average of all the experimental responses);
b_i = the estimated model coefficients;
L = the tube length;
A = the acid concentration;
F = the volumetric flow rate;
R = the fraction of organic phase fed to the reactor; and
T = the reaction temperature.

The values of the estimated coefficients and their associated statistics are summarised in Table 4.6.

Table 4.6: Estimate coefficients for the conversion of citronellal

		Value	Std. Err.	t-value	p-level
b_0	Intercept	74.120	44.63175	1.6607	0.105228
b_1	Length	-6.604	2.44716	-2.6987	0.010427
b_2	$(Length)^2$	0.607	0.15870	3.8229	0.000489
b_3	[Acid]	194.532	22.29970	8.7235	0.000000
b_4	$[Acid]^2$	-315.004	61.63324	-5.1109	0.000010
b_5	Flow Rate	0.405	0.08446	4.7936	0.000027
b_6	$(Flow\ rate)^2$	-0.004	0.00078	-5.6319	0.000002
b_7	Ratio	-207.324	19.06022	-10.8773	0.000000
b_8	$(Ratio)^2$	183.944	28.75237	6.3975	0.000000
b_9	Temp	-1.353	0.67691	-1.9988	0.053019
b_{10}	$(Temp)^2$	0.009	0.00259	3.5733	0.001001
b_{11}	(Flow rate x Length)	0.021	0.00728	2.8513	0.007082

The low p-values ($p < 0.05$) show that pipe length, acid concentration, flow rate, organic to aqueous ratio and temperature are all highly significant during the conversion of citronellal. What is noticeable from Table 4.6 is that there is a quadratic term for each variable, implying that the effect on conversion is not linear, but in fact curved and would result in an optimum/minimum (or turning point) for each individual variable. A synergistic interaction term for flow rate and tube length also exists. The presence of such an interaction term is probably not unexpected since both the flow rate and the tube length affects the residence time in the reactor tube, hence impacts on the degree of citronellal conversion.

The Analysis of Variance results for the citronellal conversion model are summarised in Table 4.7.

Table 4.7: ANOVA-Table for the citronellal conversion model

	Sums of squares	Degrees of freedom	Mean	F-value	p-level
Regress.	6635.106	11	603.1915	317.2885	P<0.000001
Residual	70.340	37	1.9011		
Total	6705.446				
R_a^2	0.987				

The high F-value and, consequently, the associated low p-value (<<<0.05) shows that the model is highly significant. The R_a^2 value (= 0.987) shows that the calculated model explains 98.6% of the observed variation in the percentage citronellal conversion.

Model validation (conversion)

All the statistics in Tables 4.6 and 4.7 and the consequent conclusions are only valid when the conditions for least squares regression are satisfied. This means that the residuals $(Y - \hat{Y})$ must be independent from each other and should follow the Gaussian distribution.

A histogram plot of the raw residuals (Figure 4.5), together with a superimposed theoretical normal distribution, shows that the experimental results are normally, or very nearly normally distributed.

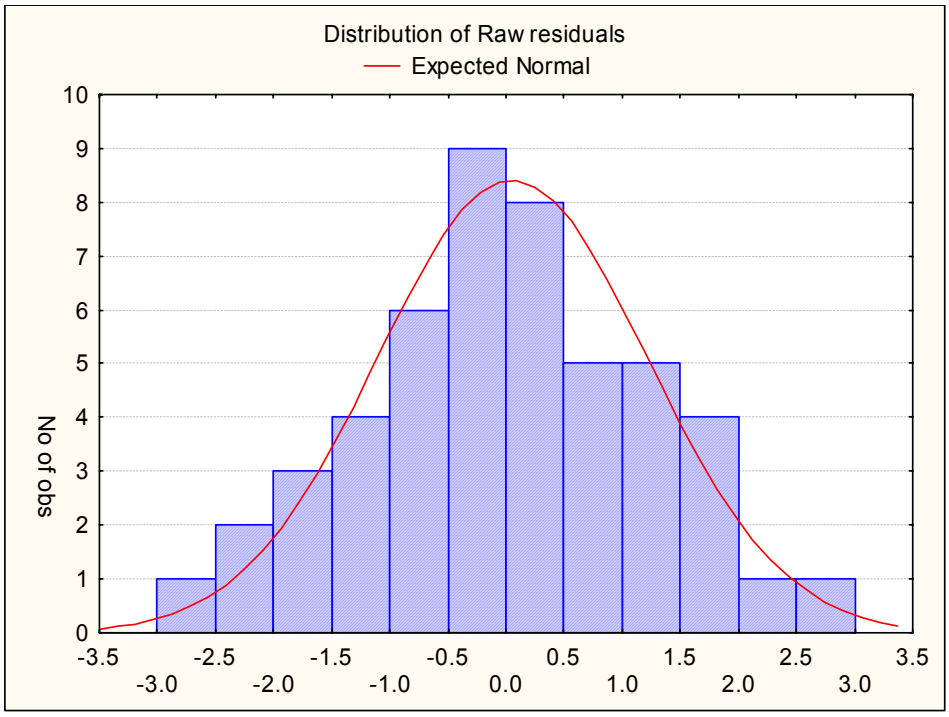


Figure 4.5: Distribution of raw residuals

This is confirmed by a plot of the raw residuals against predicted citronellal conversion values (Figure 4.6), since the points are randomly distributed around the zero line. These two analyses confirm that the statistical tests carried out are valid, and that the model may be used to interpret the effect of the experimental variables on the response (citronellal conversion).

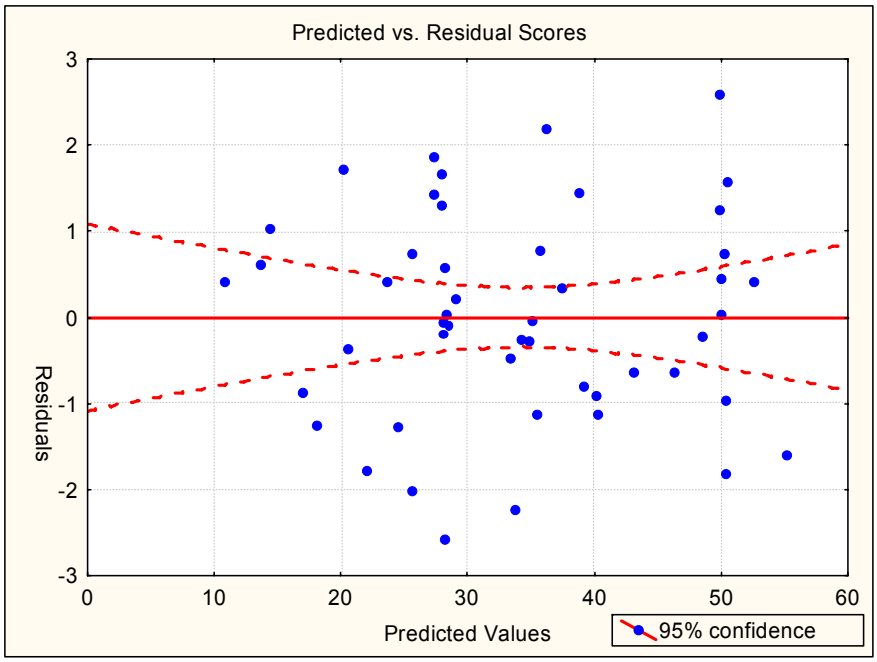


Figure 4.6: Residuals vs. Predicted Conversion

Model interpretation

Profile plots for each individual variable can be used to demonstrate the individual effect of each independent variable on the experimental response. By using the model described in Eq. [4.7] (coefficient values in Table 4.6) for the conversion of citronellal, one can change one variable at a time whilst keeping the other variables constant to view the effect of a selected variable at a time on the citronellal conversion. The levels at which the individual reaction variables were kept constant are listed in Table 4.8. It must be mentioned that the profile plots shown in Figures 4.7 – 4.11 are only applicable for the chosen constant values of those variables that were held constant and do not attempt to reflect an indication of the optimum setting of the variable in question.

Table 4.8: Constants used in the profile plots for the conversion of citronellal

Variable	Setting
Length	8
Acid concentration	0.2
Flow rate	66
Ratio (org/aq)	0.15
Temperature	123

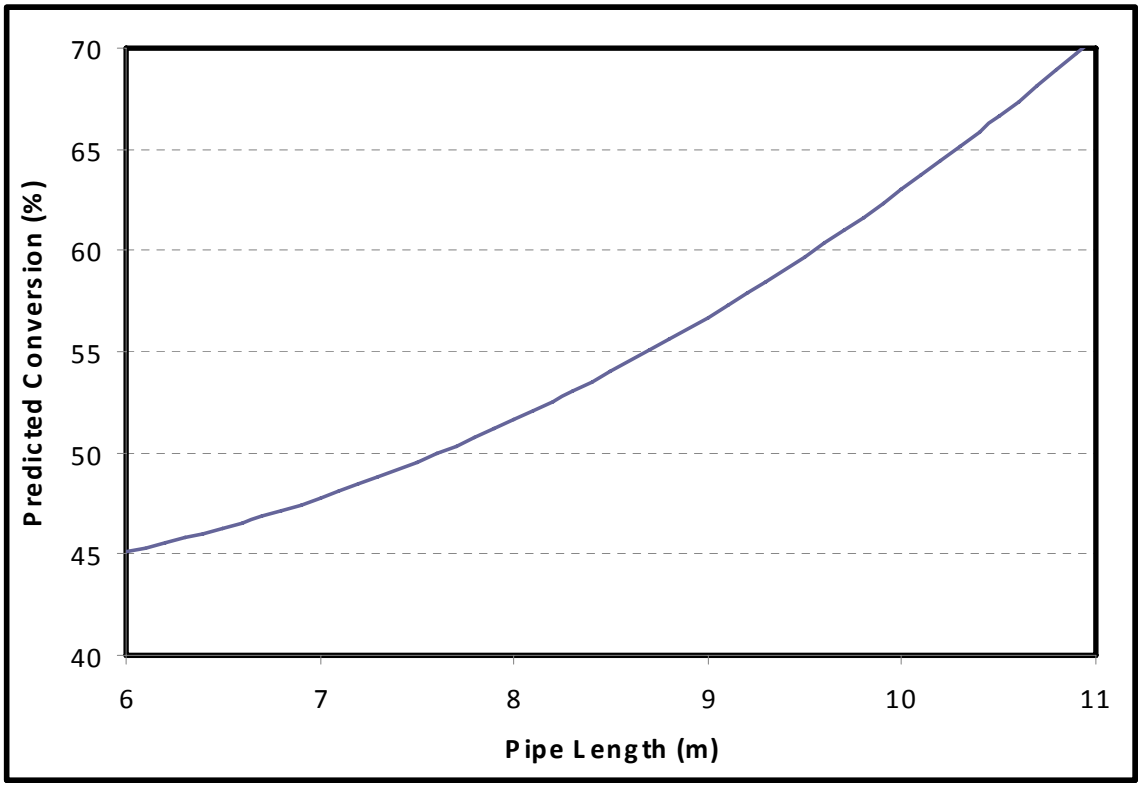


Figure 4.7: Effect of reactor length on the conversion of citronellal

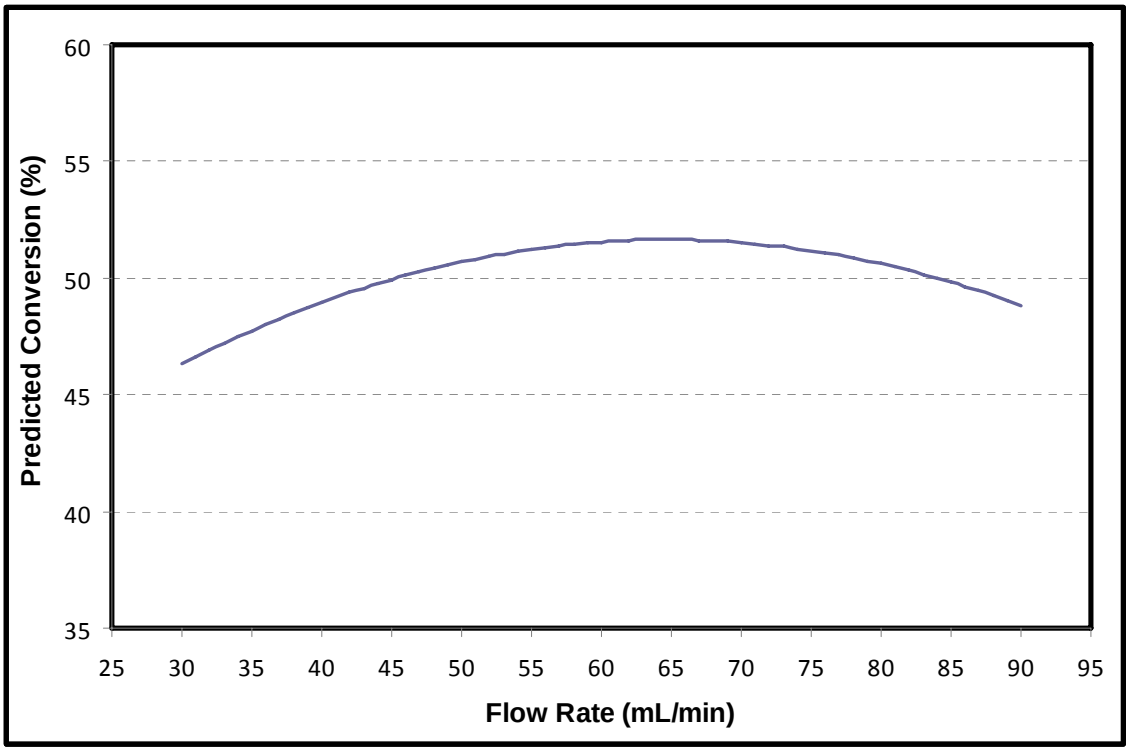


Figure 4.8: Effect of flow rate on the conversion of citronellal

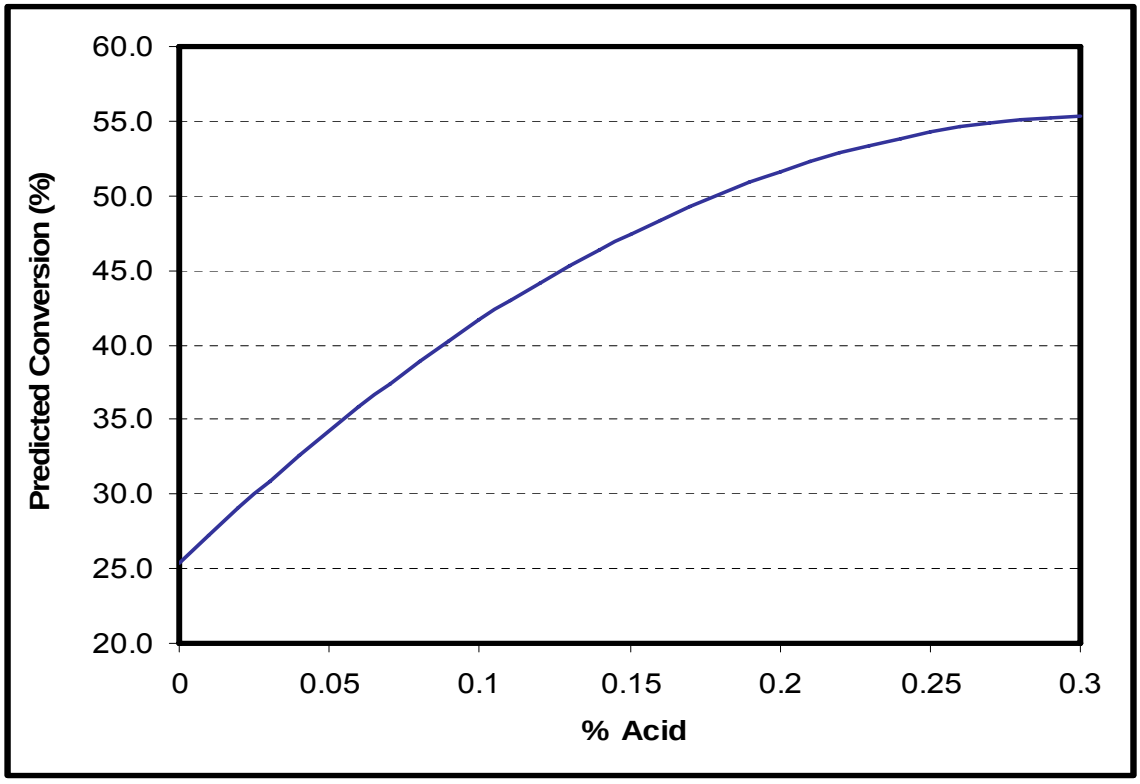


Figure 4.9: Effect of acid concentration on the conversion of citronellal

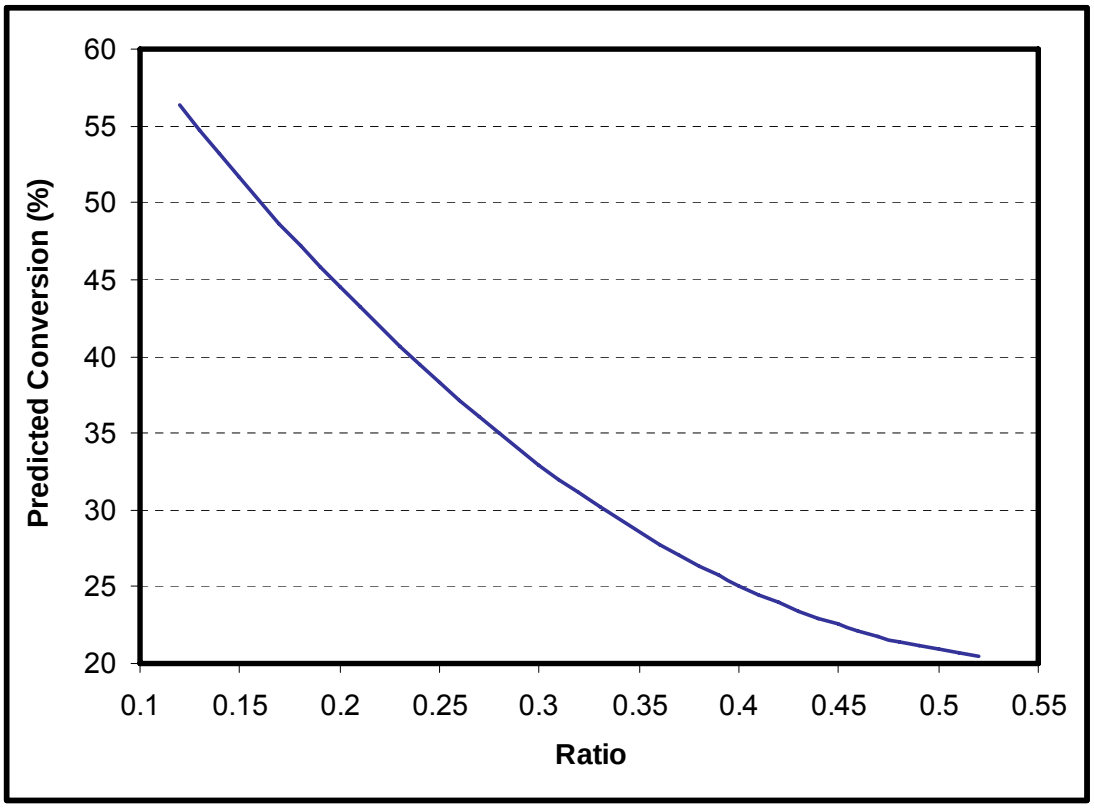


Figure 4.10: Effect of organic to aqueous ratio on the conversion of citronellal

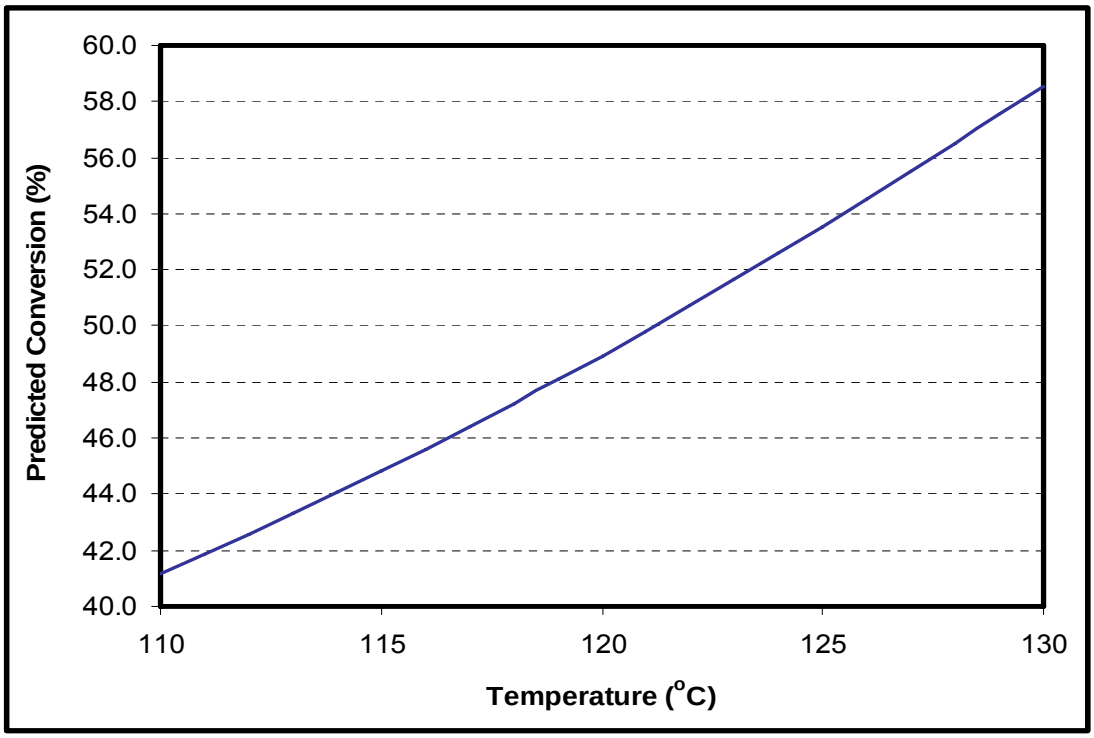


Figure 4.11: Effect of temperature on the conversion of citronellal

Figures 4.7 - 4.11 show the predicted effects of reactor length, flow rate, acid concentration, organic to aqueous ratio and temperature on the conversion of citronellal. The following observations are worth noting:

- In order to increase the conversion of citronellal one needs to increase the reactor length, which would increase the residence time for a specific reaction and allow for sufficient time for the relative conversion to occur (Figure 4.7).
- As discussed previously, the rate of conversion of citronellal is affected by the rate of mass transfer between the aqueous and organic phases, and which will be affected by the linear velocity of fluid flow (hence volumetric flow rate). Figure 4.8 shows that there exists a specific flow rate at which the level of citronellal (note, not the rate of citronellal conversion) will be maximised. In the case of this particular study, this optimum level of conversion needs to be interpreted in terms of a balance between increased mass transfer (hence rate of citronellal conversion) and residence time (which will become smaller as the flow rate, hence rate of mass transfer, increases). However, for this particular reactor, regardless of tube length, there appears to be a specific flow rate at which this balance is achieved and where the level of citronellal conversion is maximum.
- It can be seen (Figure 4.9) that increasing acid concentration increases the level of citronellal conversion. Such a result is probably not unexpected and probably reflects a higher rate of solvated H^+ transfer from the aqueous to the organic phase as a result of higher acid concentrations. This observation suggests that the assumption of pseudo first order kinetics made previously (Chapter 2) is not entirely correct as the rate constant will also depend on the acid concentration in the aqueous phase.
- By decreasing the organic to aqueous ratio (Figure 4.10), the level of citronellal conversion increases. Since the citronellal is added undiluted, this observation is not simply a concentration effect. The observed increase in citronellal conversion can possibly be ascribed to an increase in available surface area between the respective phases as the amount of organic phase is decreased

relative to the aqueous phase, thus resulting in more mass transfer (of H_3O^+) in the same reaction time.

- From Figure 4.11 it can be seen that the level of citronellal conversion (indirectly the reaction rate) increases linearly with increasing temperature instead of the expected exponential increase for true Arrhenius behaviour.[4] This observation serves as further confirmation that the reactor is operating in a mass transfer limited regime as the rate of mass transfer is not only influenced by temperature, but also other factors such as the available surface area across which mass transfer must occur.

A Pareto chart (Figure 4.12) can be used to depict the relative importance of the independent variables in the model on the experimental response.

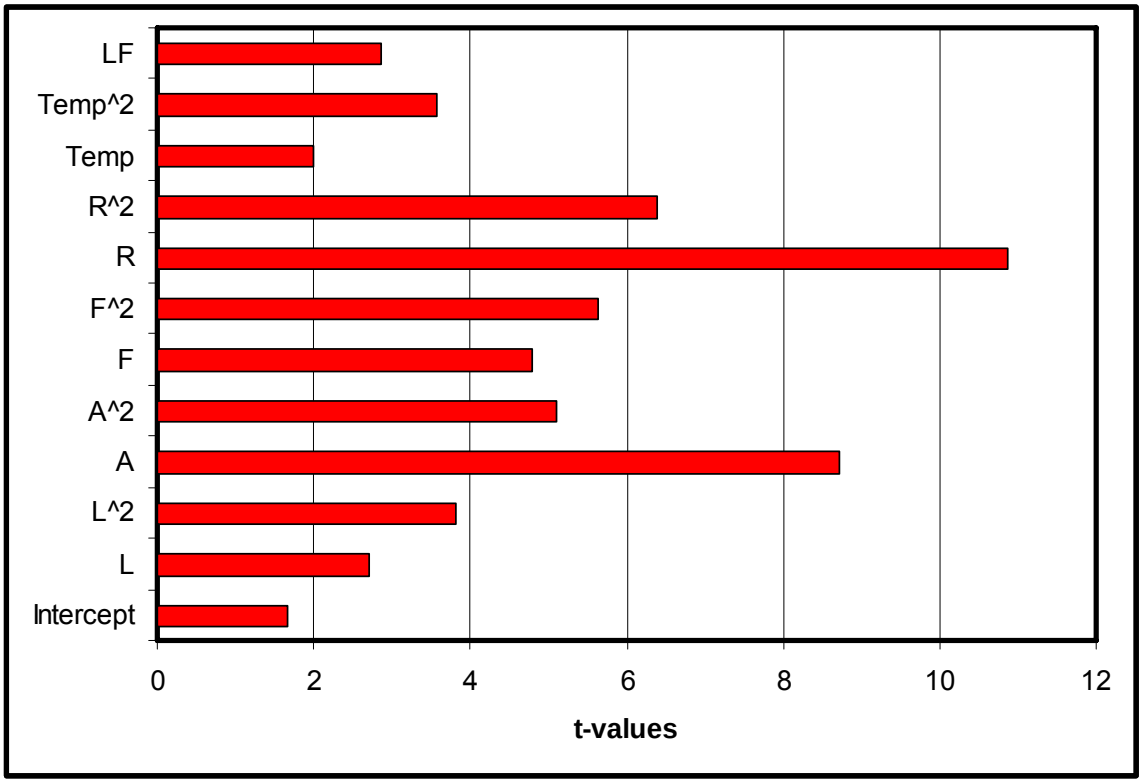


Figure 4.12: Pareto chart for citronellal conversion

From Figure 4.12 it can be seen that the organic to aqueous ratio has the largest effect on the level of citronellal conversion, followed by the acid concentration.

4.3.2.2. PMD yield model

By using stepwise regression on the data provided in Table 4.4, the best fitting model which describes the observed PMD yield is given by:

$$\hat{Y} = b_0 + b_1 L + b_2 L^2 + b_3 A + b_4 A^2 + b_5 F + b_6 F^2 + b_7 R + b_8 R^2 + b_9 T + b_{10} FL \qquad [4.8]$$

In the above model:

$\hat{Y}$ = estimated PMD yield;

b_0 = the intercept (or average of all the experimental responses);

b_i = the estimated model coefficients;

L = the tube length;

A = the acid concentration;

F = the volumetric flow rate;

R = the fraction of organic phase fed to the reactor; and

T = the reaction temperature.

The values of the estimated coefficients and their associated statistics are given in Table 4.9.

Table 4.9: The estimated coefficients and associated statistics for the PMD yield model

		Estimated coefficient (b_i)	Std. Error.	t-value	p-level
b_0	Intercept	-63.454	12.99152	-4.88429	0.000020
b_1	Length	-7.807	3.03808	-2.56985	0.014337
b_2	$(Length)^2$	0.645	0.19728	3.26693	0.002349
b_3	Acid	199.482	18.06300	11.04365	0.000000
b_4	$(Acid)^2$	-342.001	54.85156	-6.23503	0.000000
b_5	Flow Rate	0.559	0.10475	5.33958	0.000005
b_6	$(Flow\ Rate)^2$	-0.006	0.00096	-6.00455	0.000001
b_7	Ratio	-211.217	23.85409	-8.85454	0.000000
b_8	$(Ratio)^2$	204.947	35.88512	5.71121	0.000002
b_9	Temp	0.912	0.03912	23.30175	0.000000
b_{10}	(Flow Rate x Length)	0.018	0.00908	2.02884	0.049717

The low p-values ($p < 0.05$) show that the influence of reactor length, acid concentration, flow rate, organic to aqueous ratio and temperature are highly significant on the yield of PMD. As in the case of citronellal conversion, there is a quadratic term for each variable (except for temperature), implying that the effect is not linear but in fact curved and would result in an optimum for each of those variables. An interaction term for flow rate and reactor length also exists and its presence in the model is probably the same as for citronellal conversion.

The Analysis of Variance results for the PMD yield model are summarised in Table 4.10.

Table 4.10: ANOVA-Table for the PMD yield model

	Sums of	Degrees of freedom	Mean	F-value	p-level
Regress.	6244.509	10	624.4509	238.6914	p<0.000001
Residual	94.181	36	2.6161		
Total	6338.690				
R_a^2	0.982				

The high F-value and very low p-value shows that the model for PMD yield is highly significant, and the high R_a^2 value (R^2 = 0.982) shows that the model explains 98.2% of the observed variation in the percentage yield of PMD observed.

Model validation

A histogram plot of the raw residuals (Figure 4.13), together with a superimposed theoretical normal distribution, shows that the experimental results are normally, or very nearly normally distributed.

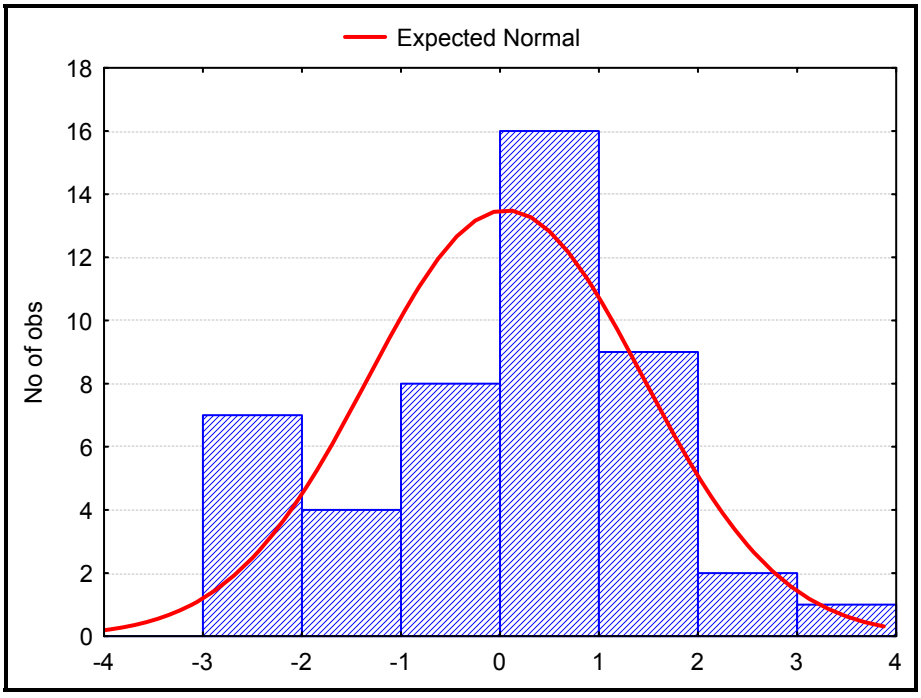


Figure 4.13: Normal distribution of raw residuals

This is confirmed by a plot of the raw residuals against predicted citronellal conversion values (Figure 4.14), since the points are randomly distributed around the zero line. These two analyses confirm that the statistical tests carried out are valid, and that the model may be used to interpret the effect of the experimental variables on the response (PMD yield).

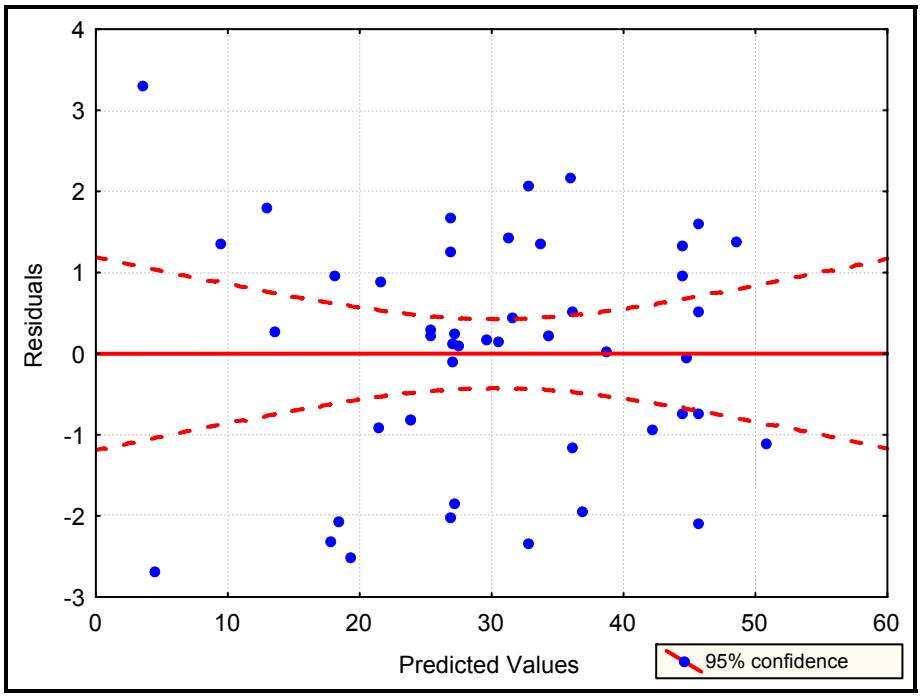


Figure 4.14: Plot of raw residuals

Model interpretation (PMD yield)

The profile plots illustrated in Figures 4.15 to 4.19 shows the effect of reactor length, flow rate, acid concentration, organic to aqueous ratio and temperature on the PMD yield. The same constants were used as shown in Table 4.8. When interpreting the profile plots, one should keep in mind that the plots do not attempt to reflect any indication of optimum settings as stated in Section 4.3.2.1.

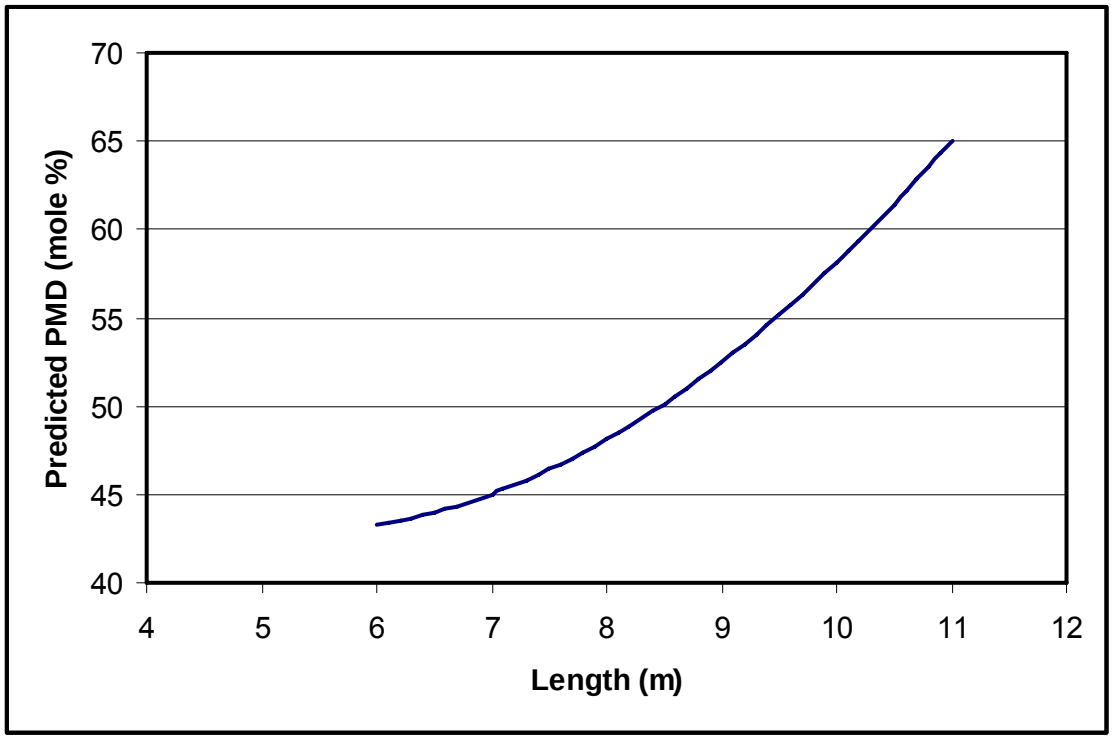


Figure 4.15: Predicted effect of reactor length on the yield of PMD

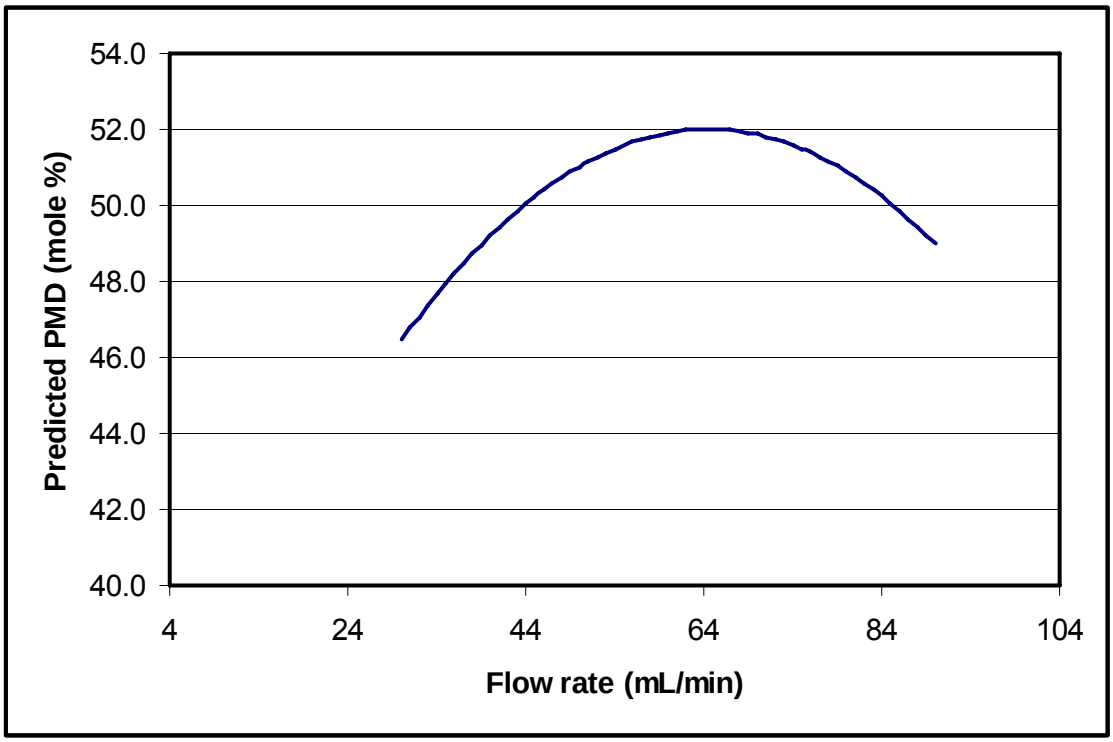


Figure 4.16: Effect of flow rate on the yield of PMD

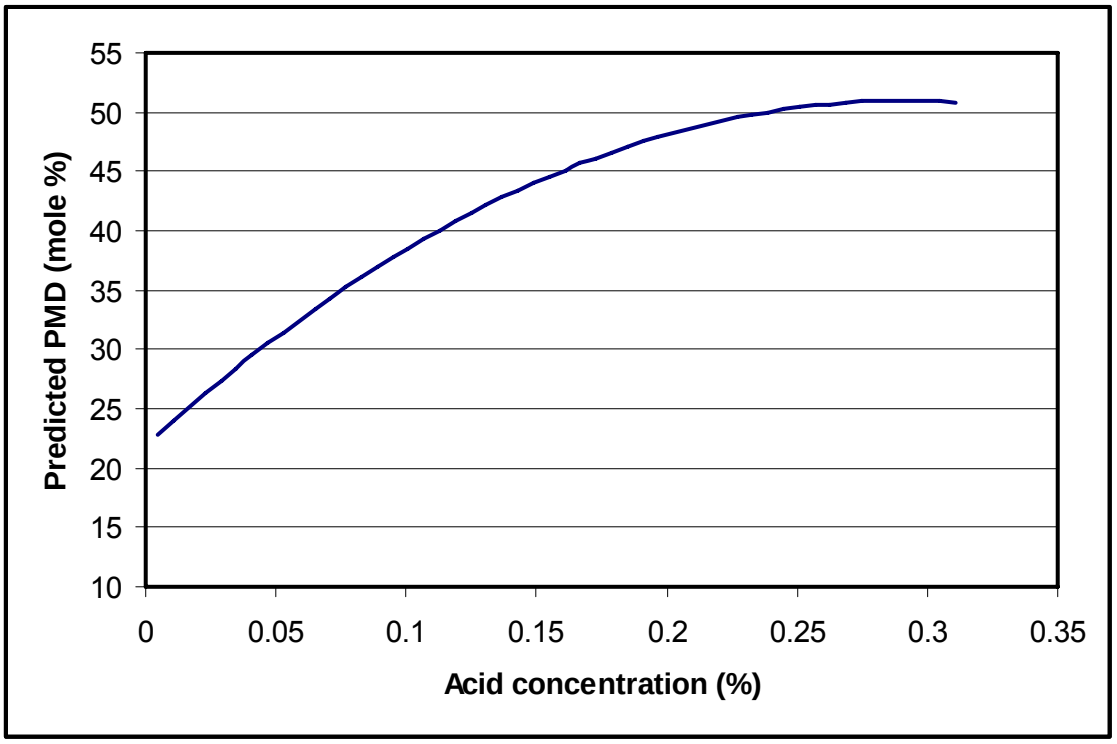


Figure 4.17: Effect of acid concentration on the yield of PMD

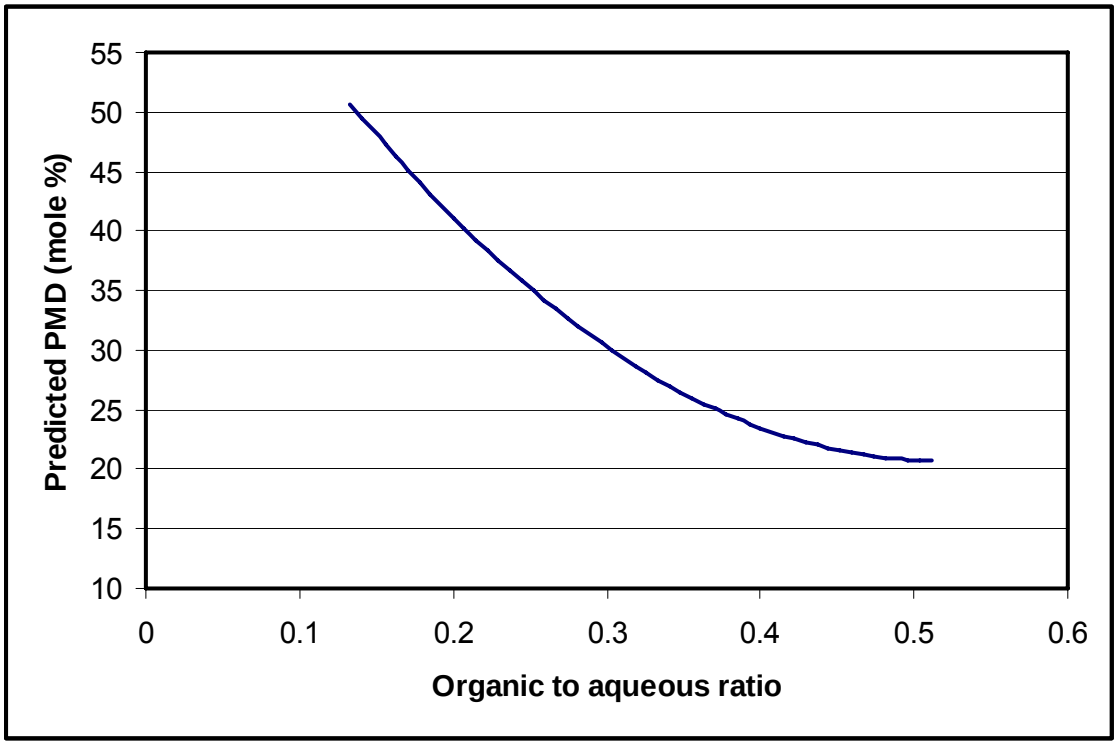


Figure 4.18: Effect of organic to aqueous ratio on the yield of PMD

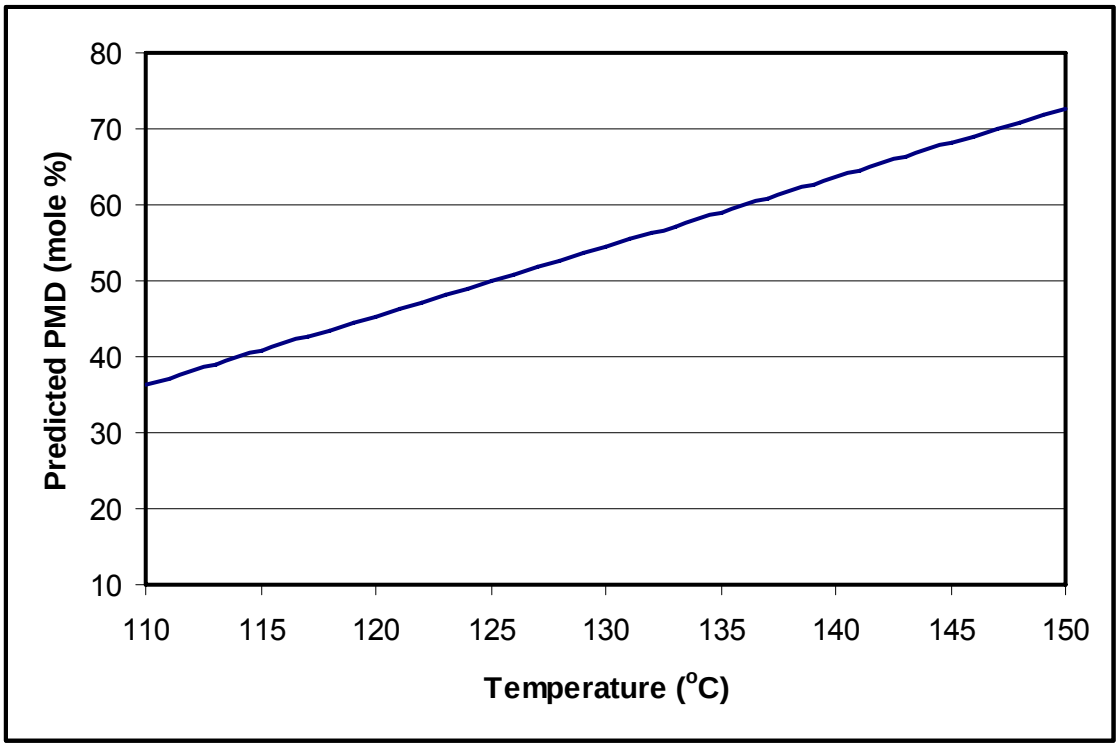


Figure 4.19: Effect of temperature on the yield of PMD

Figures 4.15 to 4.19 show the effects of reactor length, flow rate, acid concentration, organic to aqueous ratio and temperature on PMD yield. What is noteworthy is that the PMD profile plots show the same trends as that observed for the conversion of citronellal. The following observations are worth noting:

- Increasing the reactor tube length increases the PMD yield in an almost exponential fashion. This is most probably only the result of an increase in reactor residence time with increasing tube length.
- As in the case of citronellal conversion, there appears to a specific volumetric flow rate at which the yield of PMD is maximum for any given length of tube. Again this is probably an indication of a balance between increased mass transfer rate (higher reaction kinetics) and shorter residence time as the volumetric flow rate is increased.
- An increase in the acid concentration increases the yield of PMD, but the plot shown in Figure 4.17 clearly shows a “flattening-off” trend which suggests that

there will also be a specific acid concentration where the PMD yield is maximized. This is probably a reflection of the effect of higher acid concentrations on by-product formation (cf. Chapter 2), hence lower PMD yields.

- As in the case of citronellal conversion, a decrease in the fraction of organic phase fed to the reactor increases the PMD yield, and as before, is probably related to an increase in the available surface area between the respective phases.
- To increase the PMD yield, one needs to increase the temperature. This is not unexpected as an increase in the temperature would increase the reaction rate as stated by the Arrhenius principle. [4]

The Pareto chart illustrating the relative importance of each of the individual reaction variables on the PMD yield is shown in Figure 4.20.

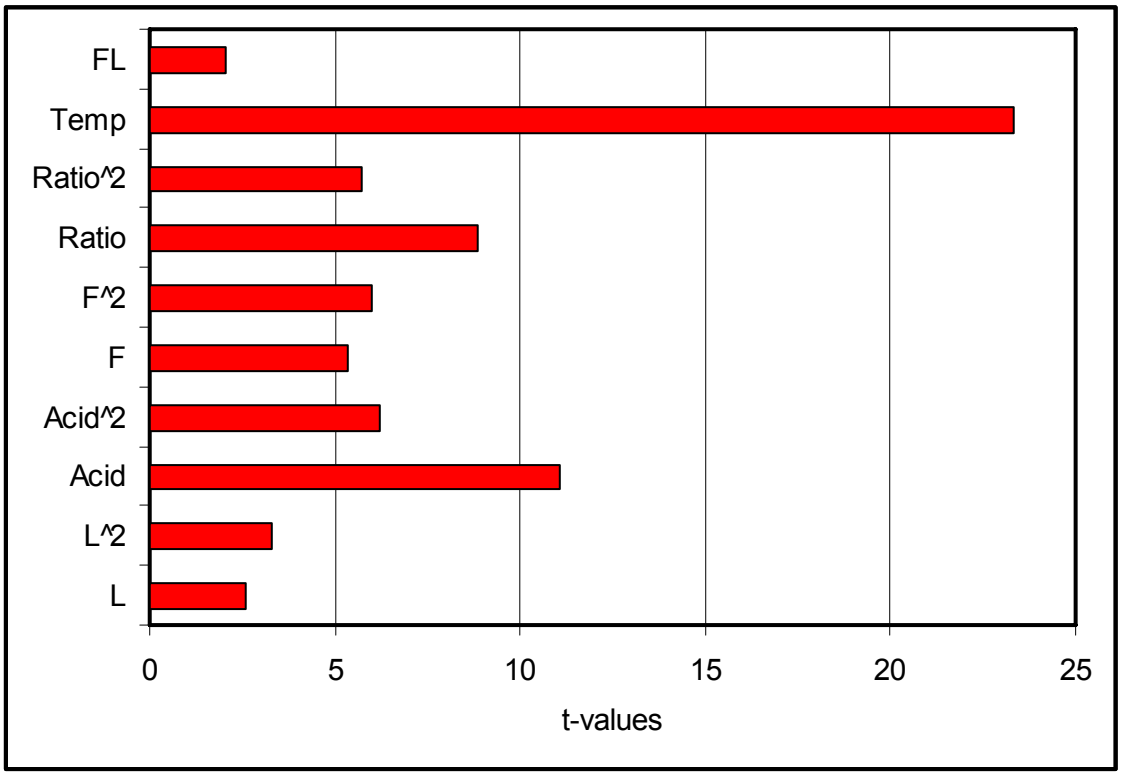


Figure 4.20: Pareto chart for PMD yield

This Pareto chart for the effect of reaction variables on the PMD yield indicates that temperature has the largest effect on the PMD yield, followed by acid concentration and the organic/aqueous ratio, respectively.

4.3.2.3. PMD-acetal yield model

The best fitting model which describes the formation of PMD-acetals, and derived as described for the previous models, is given by:

$$\hat{Y} = b_0 + b_1 L + b_2 L^2 + b_3 A + b_4 A^2 + b_5 R + b_6 R^2 + b_7 T + b_8 T^2 + b_9 RT + b_{10} AT \qquad [4.9]$$

In the above model:

$\hat{Y}$ = PMD-acetal yield;

b_0 = the intercept (or average of all the experimental responses);

b_i = the estimated model coefficients;

L = the tube length;

A = the acid concentration;

R = the fraction of organic phase fed to the reactor; and

T = the reaction temperature.

It is much more difficult to detect any effects of the independent variables on the formation of PMD-acetal since the levels of PMD-acetal produced are usually less than 1% of the product. It is therefore important to obtain very precise measurements to prevent experimental error masking the effects of the independent variables.

The values of the estimated coefficients and their associated statistics are given in the Table 4.11.

Table 4.11: Estimated coefficients for the PMD-acetal yield model

		B	Std. Err.	t-value	p-level
$\mathbf{b_0}$	Intercept	25.3405	2.934732	8.63469	0.000000
$\mathbf{b_1}$	Length	-0.3882	0.136083	-2.85267	0.007056
$\mathbf{b_2}$	$(Length)^2$	0.0259	0.008364	3.10219	0.003668
$\mathbf{b_3}$	Acid	-19.3288	4.372735	-4.42030	0.000083
$\mathbf{b_4}$	$(Acid)^2$	8.6167	2.604633	3.30823	0.002098
$\mathbf{b_5}$	Ratio	14.2789	3.713416	3.84521	0.000459
$\mathbf{b_6}$	$(Ratio)^2$	8.9718	1.712022	5.24046	0.000007
$\mathbf{b_7}$	Temp	-0.4064	0.041315	-9.83739	0.000000
$\mathbf{b_8}$	$(Temp)^2$	0.0018	0.000154	11.77983	0.000000
$\mathbf{b_9}$	RT	-0.1727	0.027219	-6.34362	0.000000
$\mathbf{b_{10}}$	AT	0.1438	0.032640	4.40423	0.000087

The low p-values ($p < 0.05$) show that reactor length, acid concentration, organic to aqueous ratio and temperature are all highly significant for the formation of PMD-acetals. Again there is a quadratic term for each effect included in the model, as well as two interaction terms: one for the interaction between the organic to aqueous ratio (R) and temperature (T), and one for the interaction between the acid concentration and temperature. The (Ratio x Temp) term is negative and indicates that the amount of PMD-acetals formed decreases as the reaction temperature and the fraction of the organic phase fed into the reactor is increased simultaneously. On the other hand, the (Acid x Temp) term is positive, which implies that the amount of PMD-acetals is increased as the acid concentration is increased at higher temperatures.

What is especially important to note from the above model is that flow rate does not seem to have a statistically significant effect on the amount of PMD-acetals formed under the conditions used for these design experiments. This is somewhat surprising

since the reduction in reactor residence time at higher volumetric flow rates alone can be expected to reduce the amount of PMD-acetals formed. The absence of a flow rate term in the above model is, therefore, probably more an indication of the relatively small size of such a term so that it cannot be discerned statistically from normal experimental error variation.

The Analysis of Variance results for the PMD-acetal yield model are summarised in Table 4.12.

Table 4.12: ANOVA-Table for the PMD-acetal yield model

	Sums of	Degrees of freedom	Mean	F-value	p-level
Regress.	4.820499	10	0.482050	66.67571	P<0.000001
Residual	0.260272	36	0.007230		
Total	5.080770				
R_a^2	0.935				

The relatively high F-value and very low p-value show that the model for PMD-acetal yield is highly significant, and the high R_a^2 value (R^2 = 0.935) shows that the model explains 93.5% of the observed variation in the percentage yield of PMD-acetals.

Model validation

A histogram plot of the raw residuals (Figure 4.21), together with a superimposed theoretical normal distribution, shows that the experimental results are normally, or very nearly normally distributed.

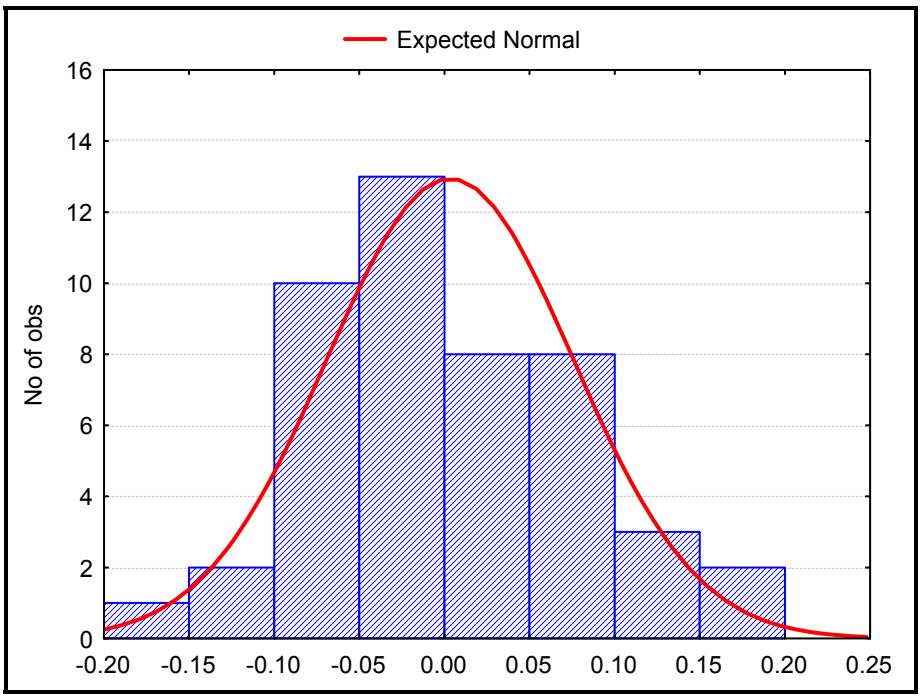


Figure 4.21: Normal distribution plot of residuals

This is confirmed by a plot of the raw residuals against predicted citronellal conversion values (Figure 4.22), since the points are reasonably randomly distributed around the zero line. To confirm normality, a separate test of normality (Kolmogoroy-Smimov test) was also carried on the PMD-acetals yield data, which confirmed normality. These analyses confirm that the statistical tests carried out are valid, and that the model may be used to interpret the effect of the experimental variables on the response (PMD-acetals yield).

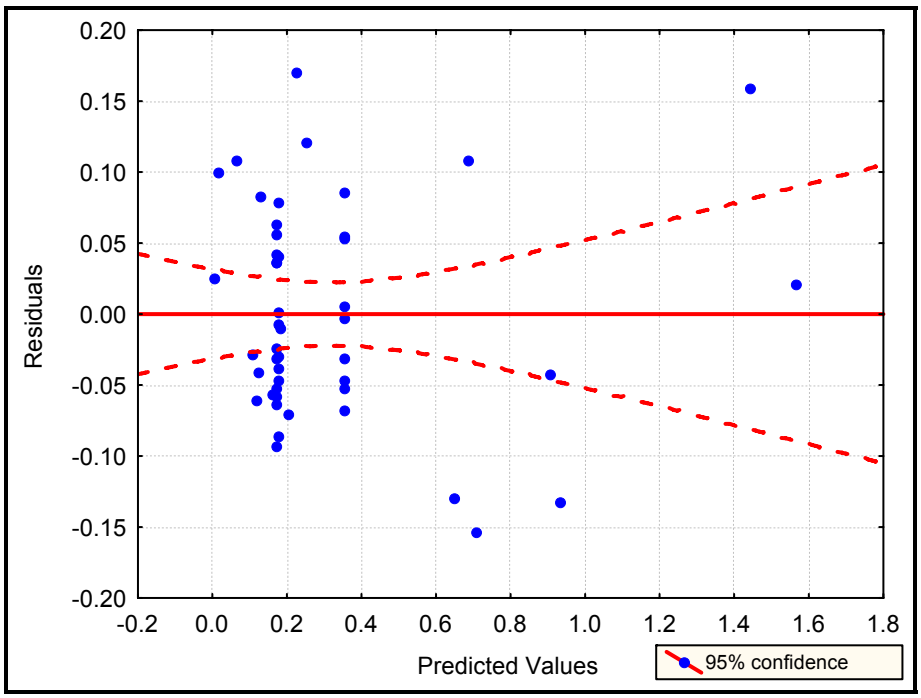


Figure 4.22: Plot of raw residuals

Model interpretation: PMD-acetals formation

The following profile plots (Figures 4.23 – 4.26), derived in exactly the same manner as for the citronellal conversion model, and using the constants given in Table 4.8, show the effect of reactor length, acid concentration, organic to aqueous ratio and reaction temperature on the percentage PMD-acetals formed during the continuous process.

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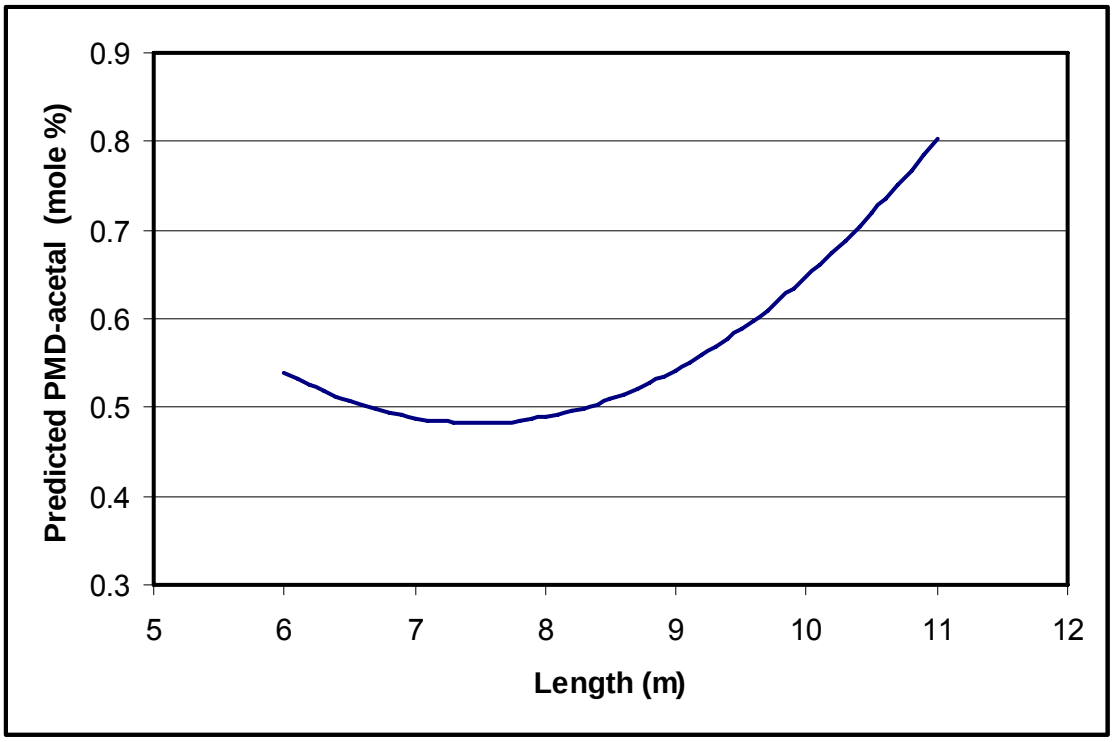

Figure 4.23: Effect of reactor length on the formation of PMD-acetals

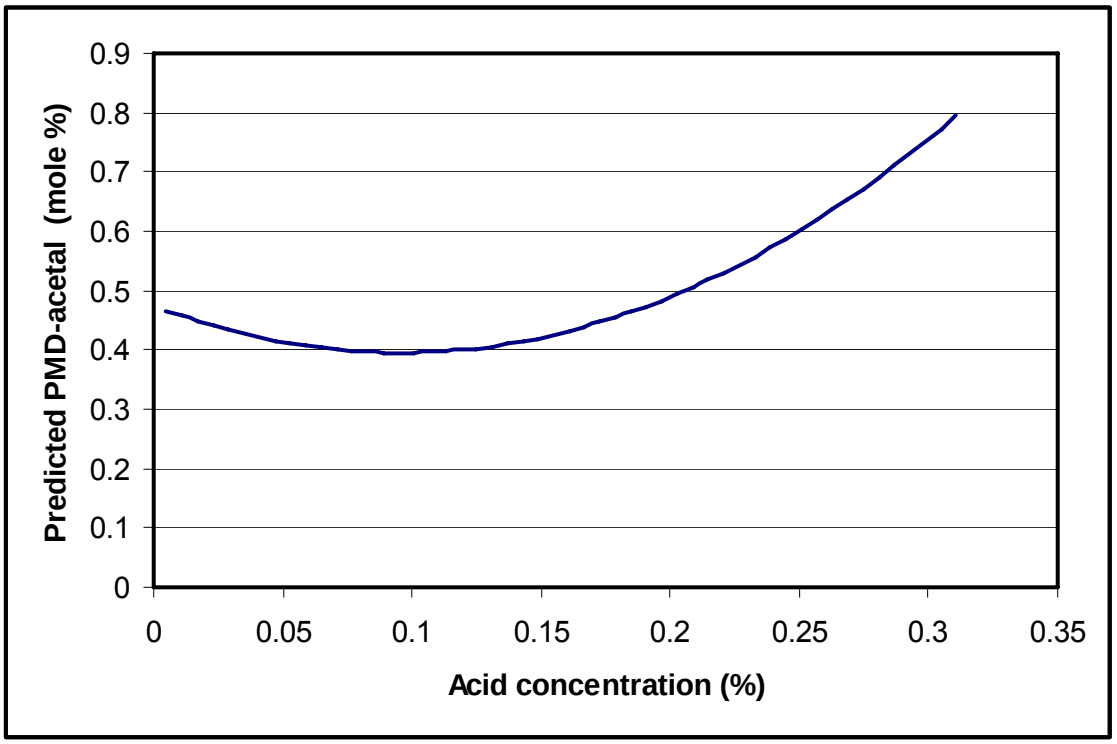

Figure 4.24: Effect of acid concentration on the formation of PMD-acetals

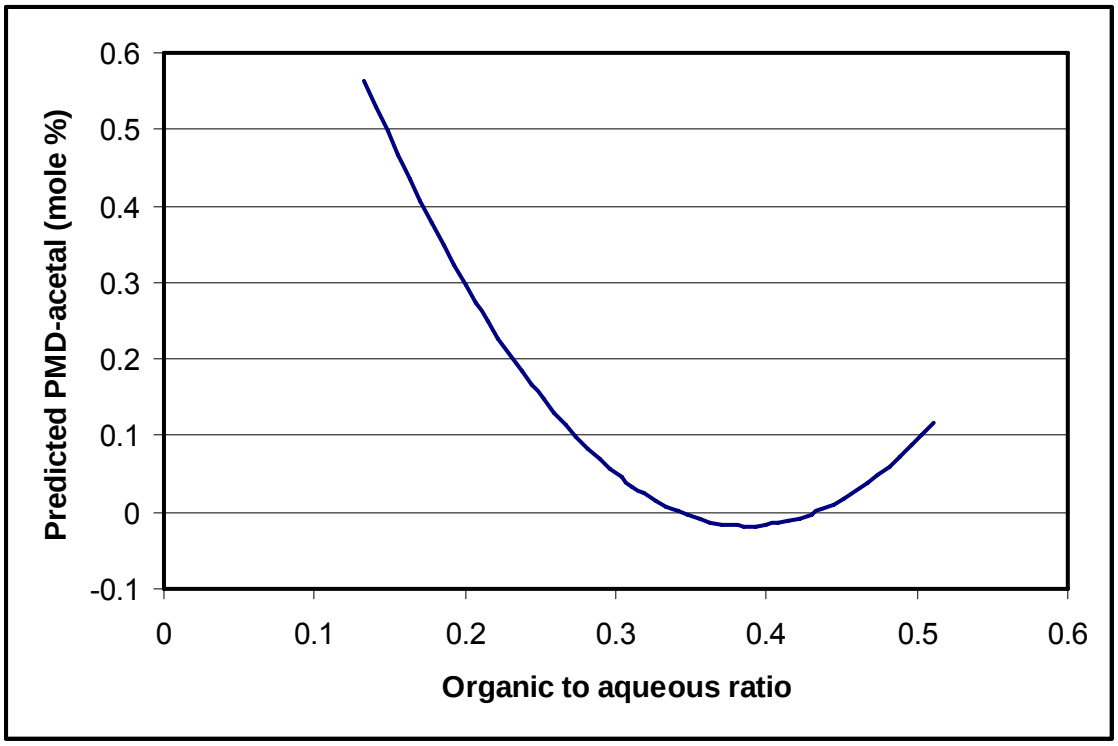

Figure 4.25: Effect of organic to aqueous ratio on the formation of PMD-acetals

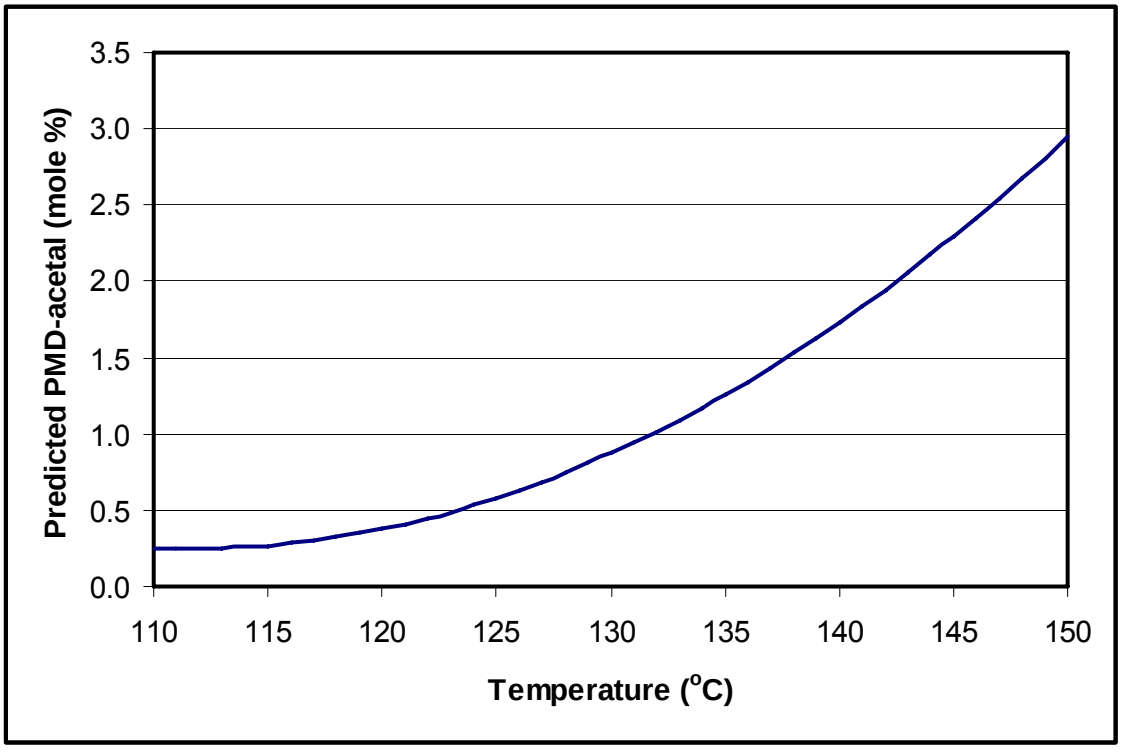

Figure 4.26: Effect of temperature on the formation of PMD-acetals

The following aspects regarding the profile plots shown in Figures 4.23– 4.26 are worth noting:

- Before commenting specifically on the trends indicated by the profile plots, one specific observation made during some of the experimental runs on the SPP rig should be made, namely the formation of a brown precipitate upon neutralization of the reaction mixture exiting the plant with $NaHCO_3$. ICP analyses of this brown precipitate confirmed the presence of Fe-oxide, which strongly suggests that under certain reaction conditions (e.g. high acid concentrations and reaction temperatures >130^{o}C), significant corrosion of the tubular walls occur. The formation of iron ions during the continuous process could result in the catalysis of PMD-acetals formation as iron is a well-known Lewis acid catalyst.[5] A comparative reaction in a batch reactor whereby a small amount of $FeSO_4$ was deliberately added to the aqueous phase of one reaction showed a small, yet significant increase in the amount of PMD-acetals formed (Table 4.13). This observation makes it particularly difficult to interpret the results for PMD-acetals formation since the presence of Fe(II) at varying concentrations (e.g. longer tube lengths, higher acid concentrations, higher temperatures) will affect the amount of PMD-acetals formed.

Table 4.13: Comparative study to evaluate the effect of $FeSO_4$ in aqueous phase

Component	Normal	0.012M $FeSO_4$-addition
Conversion (%)	85.68	84.32
PMD (%)	80.76	79.40
PMD-acetal (%)	1.20	1.39

- The profile plot for reactor tube length (Figure 4.23) suggests that there will be a specific reactor tube length where the amount of PMD-acetals formed will be a minimum (for different degrees of citronellal conversion). At longer reactor tube lengths, the amount of PMD-acetals increases, and as noted previously, this probably reflects the increase in the amount of PMD-acetals expected with increasing citronellal conversion as the reactor residence time increases. The reason for the suggested increase in PMD-acetals yield with shorter reactor tube lengths (below the point where the PMD-acetals yield reaches a minimum) is not clear but could be related to an increased experimental error at very low levels of citronellal conversions.
- In general it is observed that an increase in the acid concentration results in an increase in the amount of PMD-acetals formed, most likely as a result of a faster rate of solvated H^+ ions transfer to the organic phase to catalyze the PMD-acetal formation reaction. This proposal is supported by the fact that the model for the PMD-acetal formation includes an interaction term between acid and temperature. This is not unexpected as an increase in temperature would influence the mix-ability of the respective phases which will allow for faster mass transfer.
- What is significant is the effect of organic to aqueous ratio on the amount of PMD-acetals that are formed. It can be seen that when the fraction of organic phase fed to the reactor is increased, the amount of PMD-acetals are decreased. When the organic fraction is decreased, the amount of PMD-acetals is increased. This observation could possibly be explained in terms of the higher level of PMD formed when the organic fraction to the reactor is decreased (Figure 4.25). This suggestion is in agreement with the results of the kinetic studies (Chapter 2), which shows that the rate of PMD-acetal formation is directly affected by the concentration of PMD.
- Temperature also plays a vital role in the formation of acetals. This is not surprising as an increase in temperature would increase the reaction rate between intermediate and starting material, resulting in more PMD-acetal by-

products formed. The latter is evident as an interaction term for ratio/temperature which is included in the model for PMD-acetal formation.

The relative importance of the individual reaction variables on the formation of PMD-acetals is illustrated in Figure 4.27.

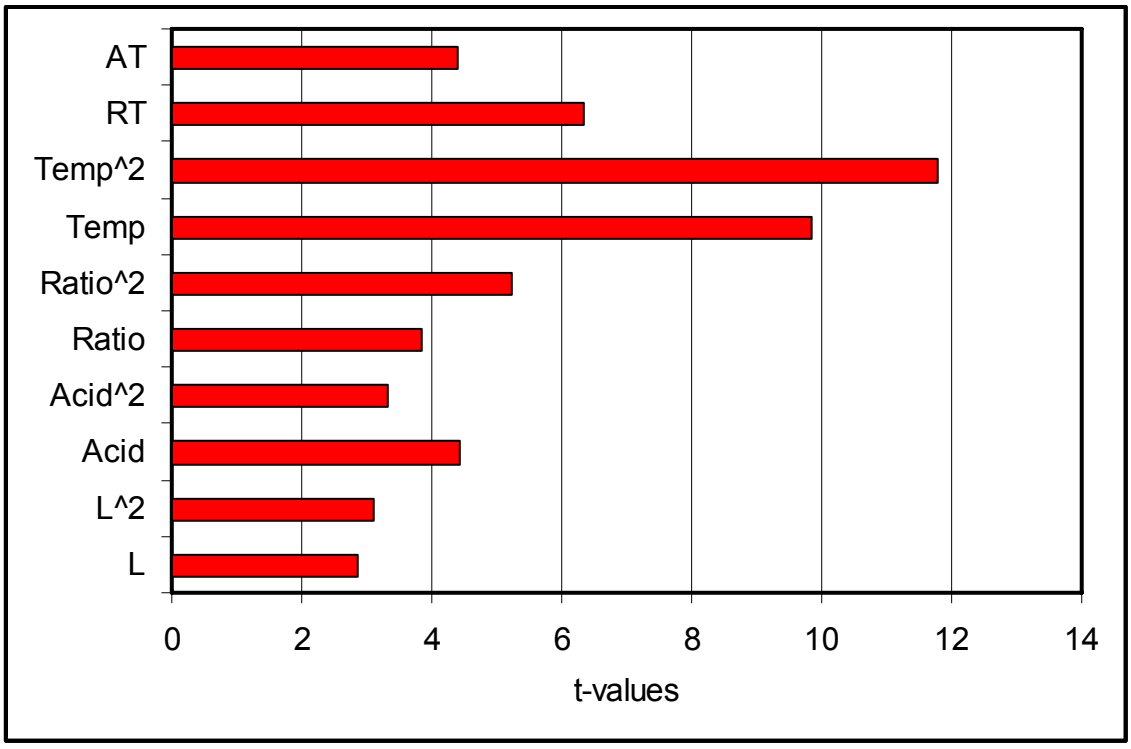

Figure 4.27: Pareto chart for % PMD-acetal

The Pareto chart shows that temperature has the largest single effect on the PMD-acetal formation.

4.3.2.4. Predicting optimum conditions using the response surface models

Careful consideration of the response surface models derived for the citronellal conversion, PMD yield, and PMD-acetals yield show that neither the “citronellal conversion” model, nor the “PMD yield” model have all the squared terms in the

model either all negative, or all positive. This implies that there is not a single turning point (maximum or minimum) for either the citronellal conversion or the PMD yield. While the squared terms of the "PMD-acetals yield" model are all positive, which means that this model does have a turning point (which is a minimum value since the squared terms are positive), it cannot be used to determine optimum conditions as not all the experimental variables are reflected for this particular model (flow rate does not significantly influence the formation of PMD-acetals).

The fact that neither of the six-dimensional response surfaces contains a local turning point does not imply that it isn't possible to create an interval for the five independent variables which gives optimum results. The reason for this is that the requirement, which is to limit the formation of PMD-acetals to a maximum of 1% while maximizing the conversion, places upper and lower limits to the five independent variables.

4.3.2.5. Confirmatory experiments

Using the profile plots for conversion, PMD and PMD-acetal formation, one could ultimately determine the settings for a range of product compositions. As it has formally been stated that a product with a purity of 99.0% and acetal content of less than 1% is desired, Equations 4.7, 4.8 and 4.9 were used to determine what reactor length, flow rate, acid concentration, organic to aqueous ratio and temperature would yield a product meeting the stated specification. In addition, such specifications would need to be met at as high a citronellal conversion as practically possible, a minimum conversion level of 40% having been set as the initial target.

Taking the PMD-acetal profile plots for the formation of acetals into consideration, random values selected for each of the five variables were entered into equations 4.7, 4.8, and 4.9 using Microsoft excel 2003. The following settings for the individual variables met the criteria set for conversion and product specifications:

Table 4.14: Predicted variable settings to meet process criteria

Variable	Setting
Length	6
Acid	0.2
Flow rate	66
Ratio	0.2
Temperature	123

Prediction	%	95% Confidence interval
Conversion	38.5	30.39-46.63
PMD	36.3	32.56-39.98
PMD-acetal	0.35	0.15-0.54

The above table shows that a reactor of 6 meters, acid concentration of 0.2%, a flow rate of 66mL/min, organic to aqueous ratio of 0.15 and a reaction temperature of 123°C, should be sufficient to produce conversions of the order of 40% with a PMD-acetal content in the final product of around 0.5%.

A confirmatory experiment was done in order to validate the predictions that were made in this section. The following results were obtained:

Table 4.15: Results for the confirmatory experiment

	%
Conversion	43.98
PMD	39.58
PMD-acetal	0.58

The table above shows that the results obtained for the confirmatory experiment with regards to the conversion and PMD falls within the confidence limits which were shown in Table 4.13. The observed value obtained for the PMD-acetals falls slightly outside the predicted range. What is also noteworthy is that the results obtained for the confirmatory experiment lies very close to the upper limits of the prediction intervals. Whether this is a coincidence is questionable and could possibly be explained by the fact that the confirmatory experiment was only conducted a period after the design was performed and that corrosion of the tubular inner walls upon standing could have increased the amount of dissolved Fe^{2+}, thereby initiating this phenomenon. However, the results are satisfactory and showed that one could meet the specification that was stipulated earlier in this thesis.

By running the continuous process at these settings (Table 4.14), i.e., 40% conversion, the amount of product that could be produced using a SPP such as the one stipulated in this study would amount to 2.6 metric tons per year. This value could be increased to the desired production capacity by using the "numbering-up" concept, which excludes tedious scale-ups commonly associated with conventional batch equipment.

4.4. Concluding remarks

In conclusion to the above results, several findings are important for the synthesis of PMD on a small production platform such as the SPP test rig. These include:

- The optimum flow rate for the reactor used in this study is 66.3mL/min; therefore the continuous process should be run at this value or higher as flow rates below this optimum value shows mass transfer limitations. However, running the reaction at a flow rate higher than 66.3ml/min would bring down the conversion of the continuous process due to the decrease in residence

time at higher flow rates, and should be compensated for by increasing the reactor length accordingly.

- By modelling the data obtained from the SPP test rig reactor, it was shown that temperature, flow rate, organic to aqueous ratio, acid concentration, and reactor length as well as temperature are highly significant in controlling the relative conversion and PMD percentages. The data indicated that in order to increase the percentage conversion and PMD, the temperature, acid concentration and reactor length should be increased, whilst the flow rate should be kept constant at 66.3mL/min, and the organic to aqueous ratio decreased.
- The results obtained for the acetal formation showed similar findings to the conclusions that were drawn in Chapter 2 for the batch studies. Firstly, if the settings for a high conversion and PMD percentage are chosen, it is indicated that these settings would result in higher acetal formation. This can be related to the concentration of PMD as it was found in Chapter 2 that the formation of the PMD-acetal is a second order reaction with regards to the PMD. Therefore, higher PMD concentrations would result in higher acetal formation. The final settings for a product of 99% purity with an acetal content of 1% would then largely depend on the settings for the acetal.
- It was indicated that the formation of a Fe^{2+} species during the synthesis of PMD could amplify relative conversions and promote the formation of the PMD-acetal. The results indicated that stainless steel would not be the material of choice for this particular synthesis and that other materials of construction should be considered, which might further improve the selectivity of the reaction.
- In view of the small production platform, the results showed that it is possible to produce a product of 99% PMD containing 1% PMD-acetal using a reactor design which consisted mainly of commercially available parts. The part lists and prices shown in Table 4.1 indicates that the plant could be built at a cost of approximately R80 000 which makes this technology extremely appealing to the small production platform concepts stipulated by the South African

government. Such a production platform would be able to produce 2.6 metric tons per year and numbering up of such reactors could increase this number to the desired production capacity.

4.5. References

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Chapter 5

p-Menthane-3,8-diol – downstream chemical processing

Abstract

The downstream processing of the PMD reaction mixture exiting from the synthesis reactor requires phase separation and neutralization of the acid catalyst solution, followed by further work-up to recover unreacted starting material and intermediates for recycle back to the synthesis reactor, and purification of crude PMD to the desired specification. During the study of the phase separation step it was shown that neutralization, prior or after phase separation, does not affect the selectivity of the PMD to such a great extent, but does influence the relative conversion due to extended contact of the catalyst with the organic phase after the reaction is terminated. Recovery of unreacted citronellal and isopulegol can be achieved by a simple vacuum evaporation step, which may either be carried out in a batch manner using traditional distillation equipment, or a continuous process using wipe-film (short path) techniques. Fractional distillation of crude PMD resulted in thermal degradation of the crude PMD mixture. In addition, results of the fractional distillation of PMD showed that it is very difficult, if not impossible, to separate the PMD from PMD-acetals to the required degree. Selective crystallization of PMD from the crude product mixture from the vacuum strip step by addition of a solvent such as heptanes or hexane in a 1:4 mass ratio with the product mixture, or recrystallisation of crude PMD, proved the best way of achieving the desired product specification.

5.1. Introduction

The reaction mixture resulting from the acid-catalysed cyclization of citronellal comprises two phases, namely the aqueous acid catalyst phase, and the organic product-containing phase. Since the reaction is deliberately not being run to completion to limit the extent of PMD-acetal formation, the organic product phase contains, apart from the PMD product, unreacted citronellal, intermediate (isopulegol) and by-product (PMD-acetal). Therefore the processing of the reaction mixture can be divided into three distinct sections (Figure 5.1):

Section A: Phase separation and neutralization (or *vice versa*);

Section B: Removal of the starting material from the crude PMD product; and

Section C: Further purification of the crude PMD in order to obtain the final product.

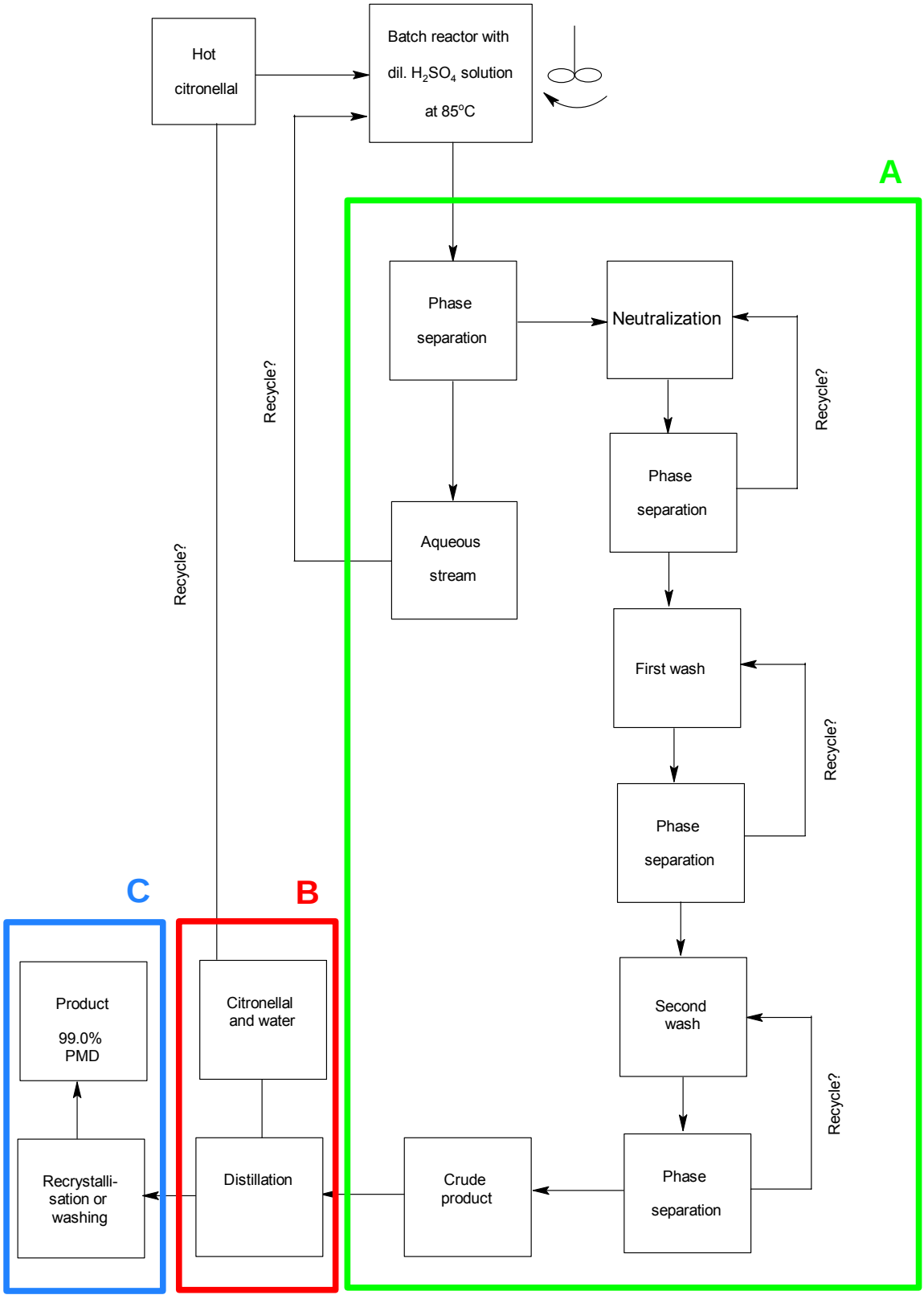


Figure 5.1: Process flow diagram for PMD

The most efficient and effective work-up and product isolation procedure will be determined by a number of factors such as the rate of phase separation (at the reaction temperature), the degree of solubility of starting material, intermediates, product and by-product in aqueous phase, the differences in boiling points, etc.

Table 5.1 summarises some of the most important properties of the various components in the reactor exit stream of direct interest to the work-up and product isolation procedure.

Table 5.1: Physical properties: summary

Compound	Melting Point (^oC)	Boiling Point (^oC)	Solubility in Water (g/100g Water at 25^oC)
Citronellal	-13.6	207.0	insoluble
Isopulegol	61-62	212.0	insoluble
***p*-Menthane-3,8-diol**	34.5	240.0	0.29
Acetal	N/A	350.0	insoluble

5.1.1. Phase separation and neutralization

The first step of the work-up and product isolation procedure is the separation of the organic and aqueous phases. There are two possibilities, namely:

A. Separation of the two phases before neutralization of the acid catalyst; and
B. Separation of the two phases after neutralization of the acid catalyst.

In the case of (A) above, the continued presence of the acid catalyst will result in further reaction after termination of the reaction since the reaction time would be increased due to inclusion of the time required for separation to occur. The extent of further reaction will be particularly problematic for reactions run at high temperatures, and will also be influenced by the rate at which the two phases separate at these

higher temperatures. In addition, at high temperatures the solubility of product in the aqueous phase will increase so that larger amounts of product will be retained in the aqueous phase. The advantage of approach (A), however, is that the aqueous phase can be recycled after adjustment of the acid catalyst concentration (see later), and the amount of aqueous waste will be reduced significantly.

In the case of (B) above, neutralisation can be carried out in the reactor so that the further reaction of substrate and/or intermediates and product can be minimised. However, this approach will produce significant amounts of waste since the volume of the aqueous phase is always larger than the volume of organic phase.

5.1.2. Removal of starting material/intermediate

Besides separation of the organic and aqueous phases, the organic phase would require further work-up, as it still contains some starting material and intermediate. It has been demonstrated in Chapter 4 that the continuous reactor is capable of producing a crude product with the PMD-acetal within specification (< 1.0%), and therefore further work-up should comprise only the removal of starting material and intermediate using techniques such as vacuum evaporation to provide the final product. If proven successful, this would be a significant improvement as the currently reported process suffers from high PMD-acetal content which requires tedious work-ups such as large-scale recrystallisations which further requires temperatures well below 0°C (-40°C).

The physical properties of the various components contained in the organic phase (Table 5.1) clearly shows that the boiling points, except for the starting material and intermediate, are well spaced and should therefore allow for easy separation of starting material and intermediate from the crude product using a simple fractional distillation technique. During such a simple fractional distillation, citronellal and isopulegol can be expected to co-distill due to the closeness of their boiling points. In previous studies,[1] it was shown that it is possible to reuse the combined

citronellal/isopulegol mixture with little effect to the selectivity of the PMD reaction. This chapter describes the results obtained for the downstream processing of the crude PMD product.

5.2. Experimental

5.2.1. Vacuum stripping of citronellal and isopulegol

Vacuum stripping of the citronellal and isopulegol from the crude PMD was performed on the 30L Büchi Chemreactor (Chapter 2, Figure 2.2) at the InnoVenton kilo-lab facility. A sufficient amount of the crude PMD mixture (directly after phase separation) was loaded into the reactor via the solid nozzle as it was too viscous for pumping or vacuum loading. The agitator was turned on and allowed to run at speed 2. The receiving vessels, receiver tubes and bottom of the primary condenser were wrapped with trace-heating tape to avoid crystallization of the distillate in the receiving system (not done for starting material stripping). The temperature of the thermal oil, which flows through the jacket of the 30L reactor, was increased to 130°C and the crude mixture was allowed to heat up to 117°C. After reaching the desired temperature, the system pressure was slowly reduced to 1kPa after which the distillation started. During the distillation process, the heat was increased in a stepwise manner in order to maintain a steady flow of distillate. The vapour temperature steadily ramped to 55°C after which it started to decrease indicating a fraction break. The evaporation process was stopped when the bottoms temperature reached 122°C, and the respective overhead and bottom fractions were weighed and recorded.

5.2.2. Vacuum distillation of crude PMD without fractionation column

Vacuum distillation of the crude PMD without using a fractionation column was performed on the 30L Büchi Chemreactor in exactly the same manner as described for the stripping of citronellal and isopulegol except that full vacuum (0.4kPa) was used. The evaporation process was stopped when the bottoms temperature reached

122°C (vapour 106.5°C), and the respective overhead and bottom fractions were weighed and recorded.

5.2.3. Steam distillation

Steam distillation of the crude PMD mixture was done on the 50L Büchi Chemreactor. A sufficient amount of crude PMD was loaded into the 50L reactor where after a sufficient amount of water added using a diaphragm pump. The amount of PMD and water depended on the run number. The mixture was heated to just above the boiling point of water where after the mixture started to distil. The distillate was collected and saved for analysis. After all the water was distilled off, the reaction mixture was cooled down to 50°C and samples of the reactor bottoms were collected for analysis. Once this was done, another 30L of water was added to the reactor pot containing the crude mixture and the distillation process repeated as previously. After the second distillation, the mixture was allowed to cool down again and more samples were collected for analysis.

5.2.4. Short path distillation

Short path distillation of the crude PMD was done on a Pilodist 500 short path evaporator. A sufficient amount of crude PMD was loaded into the feeding vessel and the temperature of this mixture maintained at 100°C via an external heating mantle. The thermal oil bath which circulates oil through the jacket of the evaporator unit itself was also set to the desired temperature, which depended on the run being conducted. All vents were closed off and the pressure of the unit slowly reduced to the desired pressure. The agitator was switched on and the tap which connects the feed tank to the evaporator was slowly opened to give a flow rate ≈0.5L per hour. When the feed tank was empty, the vacuum pump was switched off and the pressure allowed to increase to atmospheric pressure. The respective fractions were weighed and the data recorded.

5.2.5. Fractional distillation of crude PMD with short fractionation column

Molten crude PMD (30 – 40kg) was transferred to the 50L Büchi reactor by means of vacuum transfer. The agitator was set to speed 4. Trace heating tape was wrapped around the receiver tubes and vessels to keep the PMD that distilled over from crystallizing in the transfer tubes. The oil utility temperature was set to 120°C and allowed to circulate through the jacket of the 50L reactor.

The system pressure was slowly reduced to 0.4kPa. The oil utility temperature was further increased to 150°C until a steady reflux/boil of the crude PMD was observed. The fractional distillation column was allowed to equilibrate where-after samples were taken at the appropriate intervals. When the reactor temperature reached 122°C, the hot oil circulating through the reactor jacket was closed off and the distillation stopped. The vacuum was slowly raised to atmospheric pressure and the agitator stopped. The reactor bottoms were removed while the mixture was still warm (50 – 80 ^{o}C), weighed and placed in appropriate containers.

5.2.6. Recrystallisation

Hexane (250g) was added to 1000g of melted crude PMD at 60°C. The mixture was stirred well and placed in a commercially available deepfreeze at -18°C for 48 hours to allow the PMD to fully crystallize from the hexane. Once crystallized, the mother liquor was decanted and weighed. The remaining solid crystal lump was weighed and crushed until fine after which it was washed with two cold (0°C) 500g hexane portions using a vacuum filtration apparatus. After each wash the washings were weighed. Samples were taken of the recrystallised product and the respective washings for GC analysis.

5.3. Results and discussion

5.3.1. Neutralization and phase separation

In order to evaluate the difference between neutralizing the acid catalyst before or after phase separation of the aqueous phase, two identical batch reactions were carried out as previously described (Chapter 2). Thus, dilute sulphuric acid (272g of a 0.3% (v/v) solution) was added to the reactor and allowed to equilibrate until the solution reached the desired reaction temperature (85^{o}C). Citronellal (57.87g), pre-heated to 85^{o}C, was added to the reactor as a single batch, while the reactor was agitated at a stirring rate of 2000 rpm. The reaction was allowed to proceed for 7 minutes for both reactions. However, for the one reaction, 50.02g of a 2.5% (w/v) $NaHCO_3$ solution (at room temperature) was added to the reactor (whilst continuing the stirring at 2000rpm) over a period of one minute. The two phases were then allowed settle (by stopping the stirrer) for another minute before the aqueous phase was drained off. The organic phase was then washed with three portions of deionised water (50 mL), and the organic phase analysed by gas chromatography as described before.

For the second reaction, the procedure following the reaction stage was modified as follows: after eight minutes reaction period, the overhead stirrer was stopped and the reaction mixture allowed to stand for one minute to allow the two phases to separate. The aqueous phase was drained off and the organic phase was then washed with 50.02g of a 2.5% (w/v) $NaHCO_3$ solution (at room temperature), and twice with 50 mL portions of deionised water. A sample of the organic phase was then analysed by gas chromatography as described before. The results obtained for these two comparative experiments are summarised in Table 5.2.

Table 5.2: Effect of method of phase separation on product yield and quality

Run	Conditions			Responses		
	$[H_2SO_4]$ (%)	Aq/Org Ratio	Temp. (^0C)	Citronellal Conversion (%)	PMD Selectivity (%)	Acetal Selectivity (%)
1	0.3	4	85	77.12	96.81	3.17
2				87.07	97.50	2.49

Although the results in the above table may not be as conclusive as one would have hoped for, one can however see that the additional reaction time of one minute in run 2 (neutralization after phase separation) while the two phases are separating, leads to an increased conversion of substrate. Surprisingly the results of run 1 (neutralization before phase separation) gives a product of apparently poorer quality compared to the second reaction. Nevertheless, even though the results are very close to each other, it still implies that phase separation before neutralization appears to be the most attractive option since:

- It provides a product of similar or better quality; and
- It allows all or part of the separated aqueous catalyst solution to be recycled, thereby reducing waste production (on a volume basis) considerably.

5.3.2. Vacuum stripping of citronellal and isopulegol

It has been shown in Chapter 4 that the crude PMD which is produced by the SPP contains a sufficiently small amount of PMD-acetals so as to require only the removal of starting material/intermediate in order for the PMD to meet the set specifications.

Three different approaches were evaluated, namely normal batch vacuum evaporation, short path distillation, and steam distillation.

5.3.2.1. Starting material removal by batch vacuum evaporation

Batch evaporation of the citronellal/isopulegol from crude PMD was performed on the 30L Büchi Chem reactor at the Innoventon Kilo-laboratory-facility. Table 5.3 summarises the mass balance which shows the masses of the components loaded and fractions collected during the cyclization process and the batch distillation thereof.

Table 5.2: Material balance for PMD synthesis followed by vacuum stripping

Material in	Mass (Kg)	Material Out	Mass (Kg)
Water	22.53	Aq. waste	21.525
Citronellal	5.88	Neutralization waste	9.8
Sulphuric acid	0.035	Wash water 1 waste	9.59
		Wash water 2 waste	9.62
Neutralization water	9.56	Azeotrope water	0.43
Sodium bicarbonate	0.1	Recovered citronellal	1.12
Wash water 1	9.57	Crude PMD	4.7
Wash water 2	9.65	Total mass	56.785
Total mass	57.325		

Table 5.4 summarises the experimental conditions used on the 50L Büchi Chemreactor for the vacuum stripping of starting material and intermediate isopulegol.

Table 5.4: Temperatures and pressures used for the vacuum stripping

Pressure	1kPa
Final hot oil temperature	130°C
Final pot temperature	117°C
Distillate temperature	55°C

Table 5.5 summarises the relative compositions of the crude PMD prior to vacuum stripping and of the same batch following vacuum stripping.

Table 5.5: Results for the removal of citronellal using batch distillation

	Citronellal (%)	**Isopulegol (%)**	**PMD (%)**	**Acetal (%)**
Crude PMD	19.63	3.35	73.95	3.08
After stripping	2.26	0.23	93.61	3.90

Despite allowing the temperature of the crude PMD mixture to rise to 115 ^{o}C (at 1kPa), the PMD bottoms product still contained around 2.26% citronellal. Thus, while it is possible to strip citronellal from the crude PMD using a conventional batch distillation setup, complete separation is not achieved. While it is probably possible to increase either the distillation time or temperature (or both), slight discoloration of the PMD product contained in the bottom was already observed under the present conditions, implying some degradation. The slight increase in PMD-acetal in the product fraction is most likely a simple 'enrichment' as the volume of product is reduced when removing mainly citronellal.

5.3.2.2. Short Path distillation

Short path distillation permits the successful separation of heat sensitive and high boiling point materials at significantly lower temperatures due to operating pressures as low as 1 - 0.001mbar during distillation. As a consequence, the boiling points of such compounds are reduced by 300°C or more compared to the atmospheric conditions. To achieve such low operating pressures, a special orientation of evaporator surface versus condenser surface is required as the vapours have to have a maximum cross section on their way from the point of evaporation to the point of condensation in order to minimize the pressure drop across the distillation device. Furthermore, the residence time on the hot evaporator surface has to be minimized. Short-path distillation addresses the issue of pressure drop by having the condenser placed centrically inside the evaporator itself.

Batch distillation of the crude PMD using conventional setups proved to be extremely difficult as the vacuum pressures that could be reached are generally in the order of (0.4kPa) 3 mmHg, and it is required that the heating jacket temperature of the distillation setup be increased above 130°C in order for a good (0.5L/h) distillation rate to be obtained. These high temperatures lead to discolouration of the PMD held in the bottoms, which indicates that degradation occurs during the distillation at high temperatures. It was therefore decided to attempt distillation of the crude PMD using short path distillation in order to obtain purified PMD.

Two runs were performed on the short path evaporator to determine its feasibility in removing the citronellal starting material from the crude PMD. The short path settings used for the respective distillation runs are summarised in Table 5.6.

Table 5.6: Settings used for vacuum stripping using a short path distillation unit

Setting	Run 1	Run 2
Feed temperature(°C)	78.9	79.2
Feed rate (L/h)	0.5	0.5
Jacket temperature (°C)	80	90
Wiper speed (rpm)	20	20
Pressure (mmHg)	6.6	2.9

The results obtained from the two short path distillation runs for the feed, distillate, and residue are summarised in Table 5.7.

Table 5.7: Results for vacuum stripping using the short path evaporator

Fraction	Citronellal (%)	Isopulegol (%)	PMD (%)	Acetal (%)
Feed	46.19	2.73	50.48	0.59
Run 1 Distillate	88.71	4.95	6.31	0.024
Run 1 Residue	10.14	0.95	87.61	1.30
Run 2 Distillate	84.10	4.66	11.15	0.090
Run 2 Residue	6.77	0.76	91.11	1.36

The results for the short path distillation show a similar trend to the normal batch vacuum stripping with some citronellal (roughly 7-10%) and isopulegol still remaining in the bottom fraction. While successive passes through the short path evaporator

may possibly remove more citronellal and isopulegol, it is doubtful whether their complete removal will be possible. At any rate, the amount of PMD removed together with the citronellal is quite significant and recycling even larger amounts of PMD may have a negative effect on PMD-acetal formation during the synthesis reaction. As in the case of batch vacuum stripping, the increase in PMD-acetal content is probably due to the effect of enrichment.

5.3.2.3. Steam distillation

The stripping of starting material/intermediate from the crude PMD obtained after the cyclization process generally yields two phases which consists mainly of citronellal and water left over from the quench and washing steps. It was suspected that the water and citronellal forms some form of azeotrope as the initial distillate boiling temperature was lower than that observed for water and citronellal. Hence it was decided to study the effect of steam distillation on the crude mixture and to see whether it was possible to remove unreacted citronellal from the crude mixture by steam distillation at atmospheric pressure. Crude PMD which still contained some starting material was loaded into the 50L Büchi Chemreactor and a known amount of water was added. The mixture was gradually heated and distilled over to yield a water and an organic phase. Samples were taken of the overhead and bottom organic fractions, and the procedure repeated twice more. Table 5.8 summarises the mass balance for the steam distillation experiment, while Table 5.9 summarises the analytical results for the respective overhead and bottom fractions.

Table 5.8: Mass balance for the steam distillation run

Component	Distillation 1 (kg)	Distillation 2 (kg)
Water	36.68	36.705
Citronellal	9.78	9.8
c. Sulphuric acid	0.125	0.12
Water	0.885	0.88
Sodium bicarbonate	0.34	0.33
Water	2.92	2.93
Aqueous waste	-39.25	-39.315
Water (wash 1)	15.94	15.93
Water wash waste 1	-16.105	-15.36
Water (wash 2)	15.945	15.935
Water wash waste 2	-16.055	-17.015
Steam distillation water	37.05	55.045
Recovered water	-39.475	-55.35
Recovered citronellal	-1.115	-2.37
Crude PMD	-8.74	-7.575
Material balance	-1.075	0.69

Table 5.8: Composition of distillation fractions obtained for the steam distillation

	Citronellal (%)	Isopulegol (%)	PMD (%)	Acetal (%)
Crude mixture	13.17	3.45	78.10	5.39
Distillation 1	61.88	23.78	12.48	1.86
Distillation 2	77.50	18.00	4.29	0.21
Product	2.20	0.76	88.43	8.03

The above results clearly show the feasibility of stripping the citronellal and isopulegol from the crude PMD mixture using steam distillation. As in the case of vacuum evaporation, a considerable PMD carry-over is observed but, provided it does not promote PMD-acetals formation, could be recycled back to the synthesis reactor together with citronellal and isopulegol. The observed increase in PMD-acetals in the product fraction appears higher than for vacuum stripping, despite the observation that some of the PMD-acetals is also removed during the steam distillation process. The reason for the increased PMD-acetals is not quite clear, but could be related to increased PMD-acetal formation at these prolonged steam distillation periods, provided a small amount of acid catalyst remained in the crude PMD.

5.3.3. Purification by fractionation

5.3.3.1. Short path distillation of crude PMD

In view of the potential to operate the short path distillation unit on a continuous, or at least a semi-continuous basis, it was of interest to evaluate the use of short path distillation as a possible method of PMD purification. Since short path distillation works on the principle of separating components on the basis of the difference in vapour pressures rather than fractionation as in ordinary distillation, the idea was to evaluate whether PMD could be removed selectively and in high enough quantities (per pass through the short path) to make such an approach feasible. Two distillation runs were conducted on the short path distillation equipment to evaluate whether it was possible to purify PMD in this manner. Table 5.10 summarises the quantities used for the two short path evaluations, while Table 5.11 gives the analytical results for the feed and “distillate” fraction.

Table 5.10: Quantities and conditions for short path distillation

Run No	Run 1	Run 2
Feed (kg)	2.475	2.185
Initial Fraction (kg)	0	0
Main Fraction(kg)	2.375 (96%)	0.400 (18%)
Heavy fraction/residue (kg)	0.055 (2.22%)	1.748 (80%)
Evaporator jacket Temp (°C)	100	80
Pressure (mmHg)	0.09	0.3

Table 5.11: Composition of feed and fractions collected during short path distillation

		%PMD	% Acetal	% Citronellal and Isopulegol combined
Run 1	**Feed**	94.99%	3.14%	1.87%
	Main Fraction	95.53%	2.84%	1.63%
Run 2	**Feed**	94.99%	3.14%	1.87%
	Main Fraction	94.10%	1.08%	4.82%

While it was possible to distil PMD using short path distillation, no apparent separation of the by-product from the PMD seemed to occur as indicated by the compositions of the various fractions. For run 1, where 96% of the feed was distilled, the distillate only showed a 1% decrease in acetal content. In the second short path distillation run, only 18% of the feed was distilled in a single pass. This resulted in no real improvement in the PMD content, but rather a significant reduction in acetal content from 3.14% to 1.08%. Although promising results were obtained by the second run, the conditions would not result in a practical recovery of the PMD to the desired purity as only 18% of the feed was distilled.

5.3.3.2. Fractionation using batch distillation

The results obtained from the short path distillation seems to indicate that there is not a large enough difference in vapour pressures between PMD and PMD-acetal to allow for separation of the components during the continuous distillation. In order to evaluate the purification of crude PMD by traditional fractional distillation, two distillations were attempted: the first involved fractionation using an open column of ca. 1m length, and the second using a packed column that is ca. 1.5m long. The first batch vacuum fractionation was performed using the 30L Büchi Chemreactor. The setup consisted of a 30L batch reactor, which has a non-packed column of approximately 1m in length, which in turn was connected to a condenser and delivery system. The results for the fractionation attempt are shown in Tables 5.12 and 5.13.

Table 5.12: Batch distillation of crude PMD

Run	3
Feed (kg)	4.70
Initial fraction (kg)	0.315 (6.7%)
Main fraction (kg)	3.490 (74%)
Heavy fraction/ residue (kg)	0.140 (3%)
Pot temperature (°C)	117
Overhead temp (°C)	106
Pressure (mmHg)	3.0

Table 5.13: Composition of feed and fractions collected during the batch distillation

		%PMD	%PMD-acetal	% Citronellal/isopulegol combined
Run 3	Feed	96.51%	1.69%	1.80%
	Main fraction	97.51%	1.58%	0.91%

During the first distillation (run 3), 74 % of the feed was collected in the middle fraction as the main product fraction, 6.7% collected as an initial fraction, and 3% residue left undistilled. The middle product fraction showed only a 1% improvement in PMD content and 0.1% reduction in acetal concentration, indicating that virtually no separation between PMD and PMD-acetal was achieved when using an unpacked column. It was, however, noted that after the distillation, a yellow colour material was left in the bottom fraction, possibly due to degradation of the crude material as observed previously.

The second distillation involved fractional distillation of the crude PMD. Fractional distillation is a technique whereby components in a chemical mixture are separated according to their different boiling points. The temperature of the column gradually decreases along its length, which allows components with higher boiling points to condense on the column and return to solution, whilst components with lower boiling points pass through the column.

The columns are usually packed with an inert material which allows for better separation of components due to the continuous evaporation and condensation of boiling components on the packing material surfaces. In order to evaluate whether a better separation between PMD and PMD-acetals could be achieved using a packed fractional distillation column, a crude PMD sample was fractionally distilled on the 50L Büchi Chemreactor which was equipped with a 1.5m packed column using the same procedure as described for the 30L distillation. The results obtained for this distillation of PMD (Table 5.14) shows a substantial degree of separation of components. However, a careful comparison of the GC traces for the feed (Figure 5.2) and distillate (Figure 5.3) shows a significant change in the isomer distribution during this distillation process.

Table 5.14: Fractional distillation of PMD using the 50L Büchi Chemreactor

	Citronellal (%)	Isopulegol (%)	PMD (%)	PMD isomeric ratio (cis/trans)	Acetal (%)	Acetal isomeric ratio (cis/trans)
Starting material	7.9	2.75	85.1	3:2	4.3	3:1
Distillate	1.99	0.97	96.48	4:1	0.57	4:1

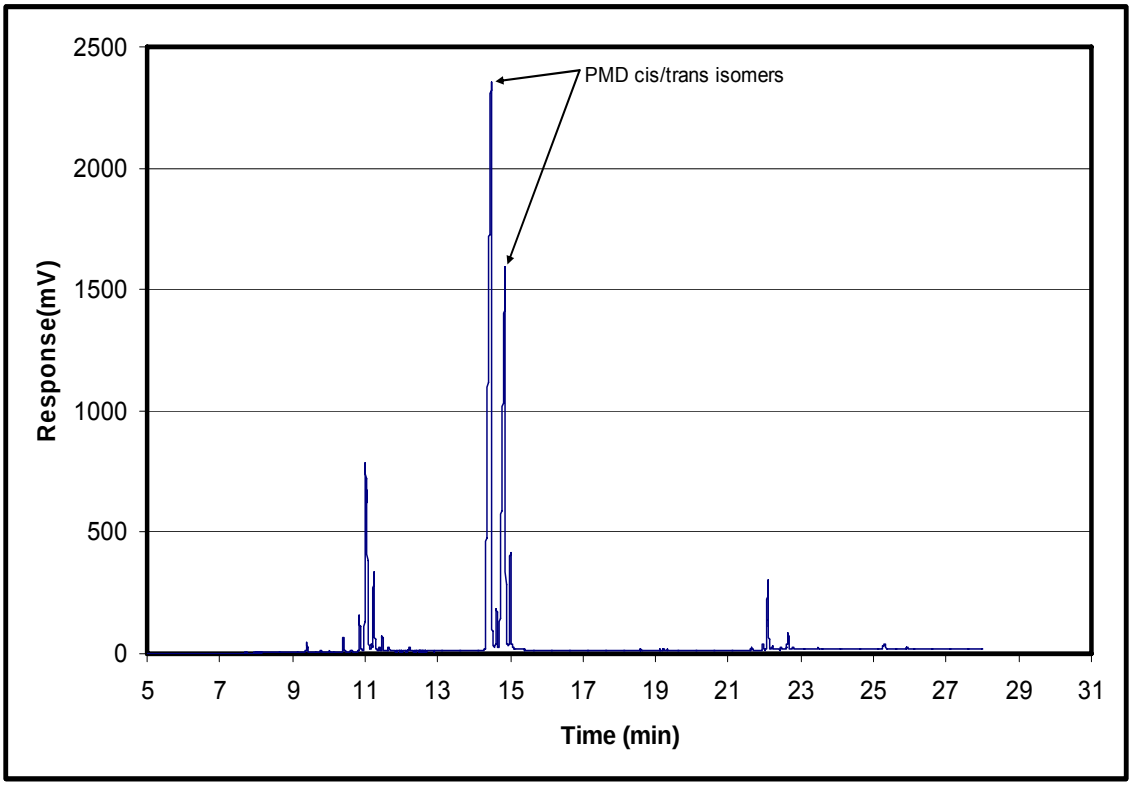


Figure 5.2: Chromatogram of feed material

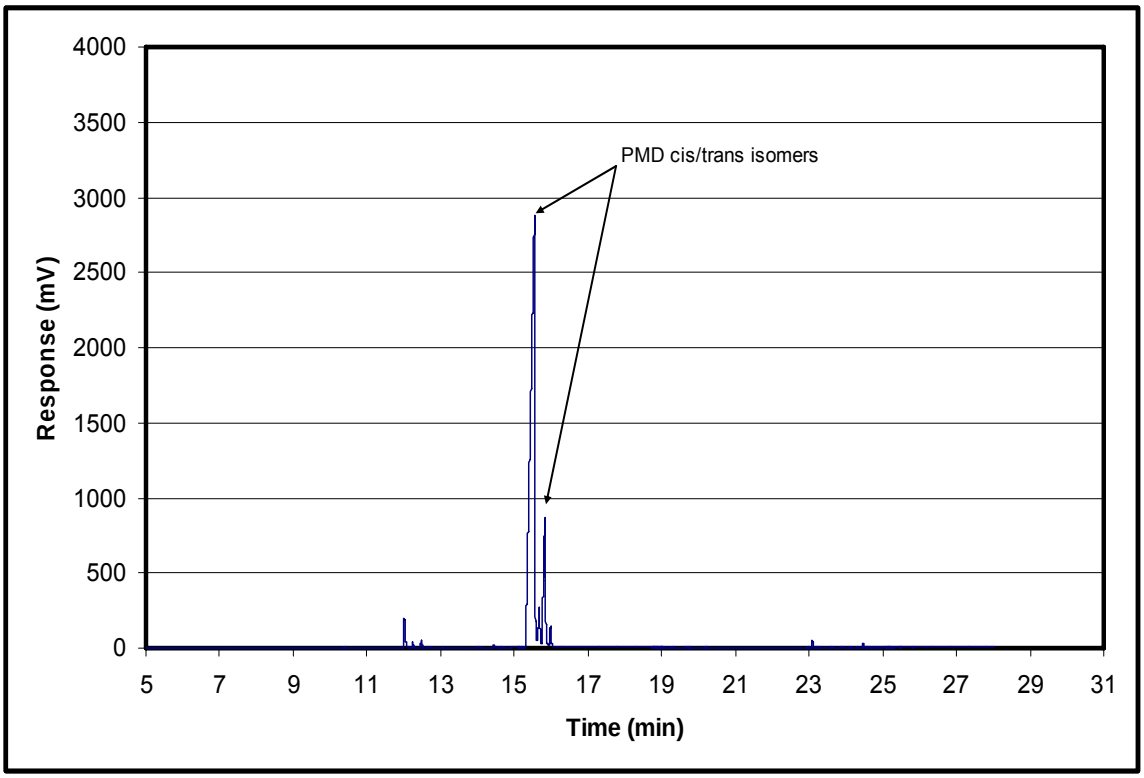
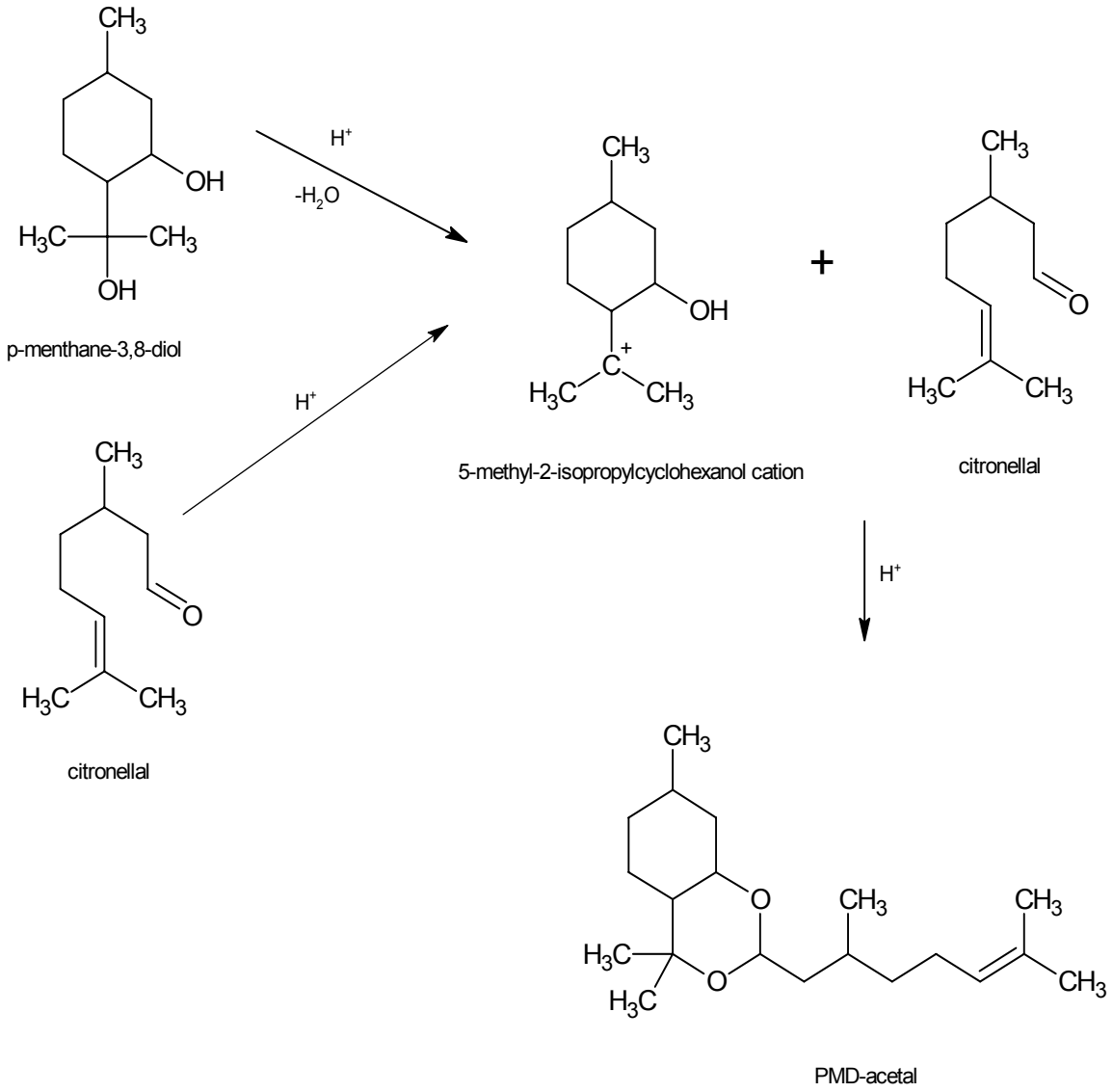


Figure 5.3: Chromatogram of the distillate

The relatively high citronellal content in the distillate is probably a result of carry-over in the condenser system since the product fraction was the first cut after the bulk of the citronellal was removed. The change in PMD isomeric ratio between the feed and the distillate could either indicate a high degree of separation efficiency in the packed column, or thermodynamic rearrangement of the trans-PMD to the more stable cis-PMD. Irrespective of which process is responsible for the change in isomeric ratio, it would appear that the higher the relative amount of trans-PMD, the better the product performs as insect repellent. Thus, any change in the isomeric distribution is not desirable from an end-use point of view.

The presence of PMD-acetals in the distillate, albeit in much reduced quantities, is rather surprising given the substantial difference in boiling points between PMD and the PMD-acetals. This certainly raises the question of the possible formation of PMD-acetals during the distillation process, since PMD-acetals may arise from either the further cyclization of citronellal, or the dehydration of PMD (to isopulegol) as shown below (Scheme 5.1).



Scheme 5.1: Reaction of the 5-methyl-2-isopropylcyclohexanol cation, which can form via citronellal or the dehydration of PMD, with starting material

It is well known that citronellal can be cyclized to isopulegol without the presence of a catalyst by ultraviolet light, or even by heat alone.[2] Such formation of PMD-acetals during distillation procedures explains why PMD, isopulegol and PMD-acetals are always present in all distillation fractions.

5.3.3.4. Recrystallisation

Isolation/purification of solid intermediates and final products are often achieved by crystallization. Under controlled conditions, crystallization generally provides excellent purification of a product and it may be essential for many fine chemicals, especially for those in the pharmaceutical industries. Crystallization on scale, however, can be very labour- and equipment-intensive, and therefore care should be taken to institute a rugged crystallization process.

In order to evaluate the effectiveness of recrystallisation as part of the purification of crude PMD, two recrystallisation experiments were carried out: the first experiment used crude PMD directly following vacuum stripping of the citronellal and isopulegol, and the second used a previously distilled sample of PMD. The first experiment is, strictly speaking, not a “recrystallisation” since it essentially involves adding solvent (hexane) to the warm crude PMD mixture following vacuum stripping, and allows crystallisation/solidification of the PMD to occur. The second experiment is a true recrystallisation since it starts with solid PMD obtained from a trial vacuum distillation as shown in Figure 5.4.

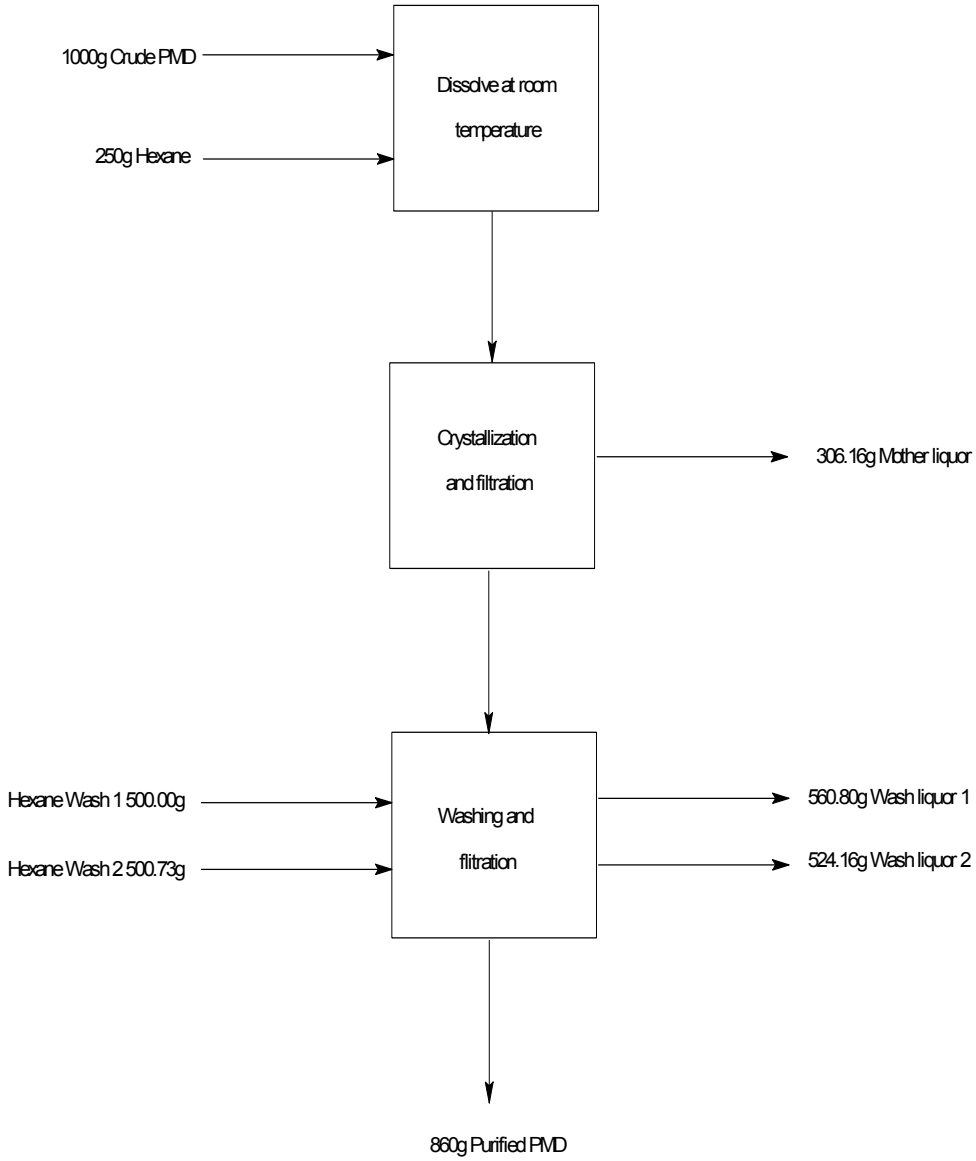


Figure 5.4: Mass balance for the crystallization process of a crude PMD sample

The results obtained for the two experiments are summarised in Table 5.15 (for the crystallization of crude PMD directly after vacuum stripping) and Table 5.16 (for the recrystallisation of previously distilled PMD).

Table 5.15: Results for the "crystallization" of crude PMD

Fraction	Component	Amount (mol %)
Crude product	Citronellal	13.32
	Isopulegol	0.11
	PMD	85.49
	PMD-acetal	1.09
Crystallized product	Citronellal	0.87
	Isopulegol	0.00
	PMD	98.62
	PMD-acetal	0.52

Table 5.16: Results for the "recrystallisation" of PMD

Process stream*	**Citronellal (%)**	**Isopulegol (%)**	**PMD (%)**	**Acetals (%)**
Crude PMD	0.77	0.28	92.75	6.20
Filter cake	0.17	0	97.47	2.36
Mother liquor	8.81	3.23	52.23	35.73
Wash 1 filter cake	0.29	0	98.58	1.14
Wash 1 liquor	1.46	0.51	92.10	5.94
Wash 2 filter cake	0	0	99.80	0.26
Wash 2 liquor	1.02	0.36	94.50	4.10

*Refer to Figure 5.4

The above results obtained show that both the selective crystallization of crude PMD (directly following vacuum stripping) and recrystallisation is very effective in purifying

PMD, even to the required specification of >99% PMD and <1.0% PMD-acetals. As in the case of distillation, unreacted starting material, isopulegol and carry-over PMD may be recovered and recycled back to the synthesis reactor.

It should be noted that the washing of respective filter cakes was performed at ambient temperatures, which undoubtedly results in significant carry-over of PMD. This may be improved significantly by using chilled solvent during the washing steps.

5.4. Concluding remarks

In conclusion to the above findings, it was shown that:

- Little difference in PMD selectivities is observed when performing neutralization prior to or after separation of the respective phases. However, increased conversions were shown to occur due to increased contact time between the aqueous and organic phase when the neutralization is performed after phase separation.
- Removal of the starting material and intermediate could be performed in one step as the result of their boiling points being very close. Removal of the starting material and intermediate using batch distillation showed that their content could be reduced down to 2% in the final product but resulted in degradation of the crude material due to the high pot temperatures and distillation times required.
- Performing a short path distillation on the crude PMD showed that it is possible to remove the starting material and intermediate from the PMD, but also indicated that an optimization study is necessary to find the conditions where starting material/intermediate can be removed without loss of too much product.
- In summary for the purification of the crude PMD, it was shown that it is very difficult, if not impossible, to separate the PMD-acetals from the crude material using both conventional and specialized distillation processes. These findings

agree fairly well with literature[3] which states that it is not possible to separate the PMD-acetals from the crude product via distillation. It should also be noted that it wasn't specified whether short path distillation or fractional distillation was ever attempted in order to purify the crude product and that no literature relating to the purification of crude PMD could be found.

- It was found that the crude PMD could be recrystallised to obtain a product which meets the specifications that was set earlier on in this thesis. The process consisted of only one crystallisation step and two washings, which demonstrates that a high yield can be reached with the first crop which also characterizes a good recrystallisation process. Although recrystallisation would appear to be the best route at first glance, one should consider the time it takes for nucleation to occur which at the bench scale proves to be very inconsistent. Recrystallisation would also require specialized equipment for washing and drying of the product, and a production facility which has access to a utility system that would be able to chill reagents down below 0°C to induce nucleation.

5.5. References

1. B. Mphulhu, M.Tech dissertation, NMMU, (2007).
2. E.J. Lenardoa, G. Jacob, Tetrahedron 63, 6671-6712, (2007).
3. Y.Yuasa, H. Tsuruta, Org. Process Res. Dev., (Technical Note), 4(3), pg159-161, (2000).

Chapter 6

Summary and concluding remarks

The synthesis of p-menthane-3,8-diol was investigated using conventional batch equipment, a micro-structured reactor and a packed tubular reactor (SPP). The goal of the study was to compare the performance of various technologies and determine whether it would be possible to produce PMD in a continuous manner while meeting a specific product specification, namely a minimum PMD content of 99.0%, and less than 1.0% PMD-acetals.

The rationale for evaluating a continuous process that could be "scaled-up" by a process of "numbering-up" a smaller production unit was related to the uncertainty in terms of the potential volumes of the p-menthane-3,8-diol that would be required should the insect repellent formulations as patented be commercially successful, as well as the constraints associated with the scale-up of traditional batch processes. Batch production processes are inherently inflexible with respect to production capacity since the size of the reactor often determines production capacity. As a result, over-designing of the reactor size often occurs based on demand volume expectations. In multi-product plants, a much larger than required reactor is often used in a campaign-style production mode (where more batches can be run to increase volumes). On the other hand, continuous processes based on a SPP such as contemplated in this study provide much more flexibility, especially when considering the modern approach to scale-up of continuous processing in the fine chemical industry by a system of "numbering-up" of smaller production units as product demand increases. The advantage of numbering up is also reflected in the fact that one can remove a SPP-unit for maintenance whilst the rest of the SPP-units continue production, whereby batch processes commonly have to shut down for maintenance hence discontinuing production. Also, the amount of capital required to start up a SPP is much less than the cost commonly associated with installation and

running costs of batch equipment. In many instances, a continuous process has a distinct technical advantage with respect to product quality and also provides better safety to the production facility since smaller volumes are involved.

6.1. Batch process

By studying the synthesis of PMD in a conventional batch reactor, it was shown that the formation of PMD from citronellal occurs via an intra-molecular Prins reaction that results in the formation of both the desired PMD product, as well as the partially hydrated isopulegol. Kinetic studies confirmed the existence of a complicated kinetic model for the formation of PMD from citronellal. The reaction displays typical pseudo-first order kinetics up to citronellal conversions of about 70%. The reaction obeys the Arrhenius principle, which implies that performing the synthesis in the absence of a reaction solvent (e.g. to improve mass transfer) would be desirable, and that an increase in reaction temperature would significantly reduce reactor residence times (and consequently the final reactor size). It was shown that at higher citronellal conversions (>70%), the kinetic model becomes inherently complicated due to the formation of several side reactions which include:

- The dehydration of the PMD product under acid catalysis, essentially setting up an equilibrium between PMD and isopulegol; and
- The reaction of the starting material with an activated intermediate, most probably the 5-methyl-2-isopropylcyclohexanol cation, to form PMD-acetals.

The 5-methyl-2-isopropylcyclohexanol cation intermediate can be formed both directly from citronellal during the cyclization reaction, as well as from PMD during its dehydration to Isopulegol, and therefore implies that the rate and extent of PMD-acetal formation will increase at higher PMD concentrations (or alternatively, higher citronellal conversions). This was confirmed by the kinetic studies which indicated that the formation of the PMD-acetal was second order with regards to PMD. In

summary, the kinetic results imply that operation of the reaction under conditions of high temperature will favour the formation of the desired di-hydrated PMD, and the degree of PMD-acetal formation would be kept to a minimum when the conversion is restricted.

Preliminary scale-up tests of the batch synthesis process demonstrated the difficulty of achieving desired processing parameters such as a desired degree of mixing and effective reagent dosing. The results obtained from the trial scale-up runs indicated that achieving both a high throughput, as well as a product with desired specifications will not be easily achieved using a conventional batch process.

6.2. Continuous process

A commercially available micro-structured reactor was used to determine whether it is possible to perform the PMD reaction as a continuous process. The results obtained from the study showed that the use of a micro-mixer such as the caterpillar micro-mixer did not provide enough residence time in order for desirable conversions (≈40%) to be obtained. In order to overcome this constraint, the micro-mixer was combined with delay loops of different thicknesses and lengths to give increasing residence times. In addition, the synthesis was carried out with increasing reaction temperatures so as to achieve improved reaction rates. The results indicated that the conversion of citronellal could be improved significantly under conditions of high temperature and pressure. However, when the degree of conversion obtained in open tubes are compared to the expected conversions for a well-stirred batch reactor operating under true kinetic control (no mass transfer limitations), the degree of conversion was extremely poor due to poor dispersion of the organic phase in the aqueous phase, thus causing poor mass transfer. To use open tubes as the reactor device would require either too thin a tube or too long a tube to ensure proper turbulent mixing to be practical.

By packing selected delay loops with inert SiC particles, the mass transfer between the organic and aqueous phases could be improved substantially, as reflected in the increased conversion of citronellal. Despite the fact that the packed tubes were still operating in a mass transfer limited domain, increasing the reaction temperature (and consequently the pressure) to 115^{o}C resulted in conversion levels far exceeding what could be achieved at the "optimum" batch reactor conditions at comparable residence times. It was also shown that replacing the caterpillar micro-mixer with a commercially available T-piece did not affect the results due to the continuous mixing of the reaction phases in the packed tube.

6.3. Small production platform

From the observations made during the study performed on the OSP, a continuous reactor (SPP-rig) was designed and constructed from commercially available components at the cost of approximately R40K. The continuous process on the SPP-rig was studied using advanced statistical techniques to investigate the effect of variables such as temperature, acid concentration, reactor length, flow rate and the organic to aqueous ratio on the selectivity of the PMD reaction. Three mathematical models were derived, which were used to predict the concentration of citronellal, PMD and PMD-acetals at any set of conditions when using the SPP-rig. The models showed the existence of an apparent optimum flow rate for the SPP-rig, which probably relates to a balance between improved reaction rates with an increase in mixing efficiency (mass transfer) and the decrease in reactor residence time with increasing flow rates. At this apparent optimum flow rate, the continuous process still operates in a mass transfer limited regime and conversions are significantly lower than what is expected from the reaction kinetics This, however, highlights the potential to improve the already significant performance of the SPP-rig if the process can be moved into a mass transfer limitless region (e.g. by using stronger pumps to achieve higher flow rates) which could improve the conversion and selectivity of the PMD reaction even further. It was shown that temperature, flow rate, acid

concentration, organic to aqueous ratio and reactor length are highly significant in controlling the citronellal conversion, PMD and PMD-acetal yields, and selectivity during the reaction.

As in the case of the batch process, high citronellal conversions (or PMD yields) result in higher PMD-acetal yields. The final values of experimental settings to achieve a product containing a minimum of 99% PMD with a PMD-acetal content of <1.0% therefore largely depends on the settings required to limit the PMD-acetal yield to below 1.0%.

The formation of a brown precipitate during the neutralization step of reaction mixtures carried out using the SPP-rig showed that corrosion of the inner walls of the SPP-rig was occurring under certain conditions. The formation of Fe^{2+} ions, which could function as Lewis-acid catalysts, possibly results in the formation of larger amounts of PMD-acetals as shown by comparative experiments where $FeSO_4$ was deliberately added to the reaction mixture. These results indicated that stainless steel would not be a suitable construction material for the final commercial SPP reactor system and that other materials of construction should be considered. Such a change in construction material may further improve the selectivity of the reaction.

6.4. Downstream processing

Investigations made with regards to the isolation and purification of the crude PMD showed that neutralization, prior to or after phase separation does not affect the selectivity of the PMD to such a great extent, but does influence the relative conversion due to extended contact of the catalyst with the organic phase after the reaction was terminated. Thus, phase separation without prior neutralization of the acid catalyst allows for the recycle of the acid phase and decreases the amount of waste that would be generated during the PMD process.

It was also demonstrated that a sufficient amount of starting material could be removed from the crude PMD using short path evaporation, and that the PMD could be purified to the desired specification (>99% PMD and <1.0% PMD-acetals) by crystallisation from n-heptane at -18°C. Attempts to purify the crude PMD using distillation techniques proved to be extremely difficult if not impossible.

6.5. Comparative analysis

By combining the findings from the batch process, OSP, SPP and downstream processing, it is possible to structure a process flow diagram which would be appropriate for the production of PMD of suitable grade at commercial scales. In summary, the following findings are emphasized:

- The batch studies showed that the conversion of the reaction should be reduced in order to limit the formation of PMD-acetals and that the reaction temperature should be increased to decrease the reaction time.
- The SPP-rig, when operated under the “optimum” conditions (for the particular reactor used – tube diameter and relatively low flow rates), will produce an approximate 44% citronellal conversion, with a 90.1% PMD selectivity and a 1.3% PMD-acetal selectivity.
- Following phase separation of the reactor exit stream, down stream processing of the crude product to a specification of >99.0% PMD, and <1.0% PMD-acetals may be achieved by vacuum stripping of the remaining starting material and isopulegol by short path evaporation, followed by selective crystallization of PMD by adding a solvent such as hexane or heptane to the warm mixture (in a ratio solvent:crude product of 1:4) and cooling.

Combining these findings, the following process flow diagram can be constructed:

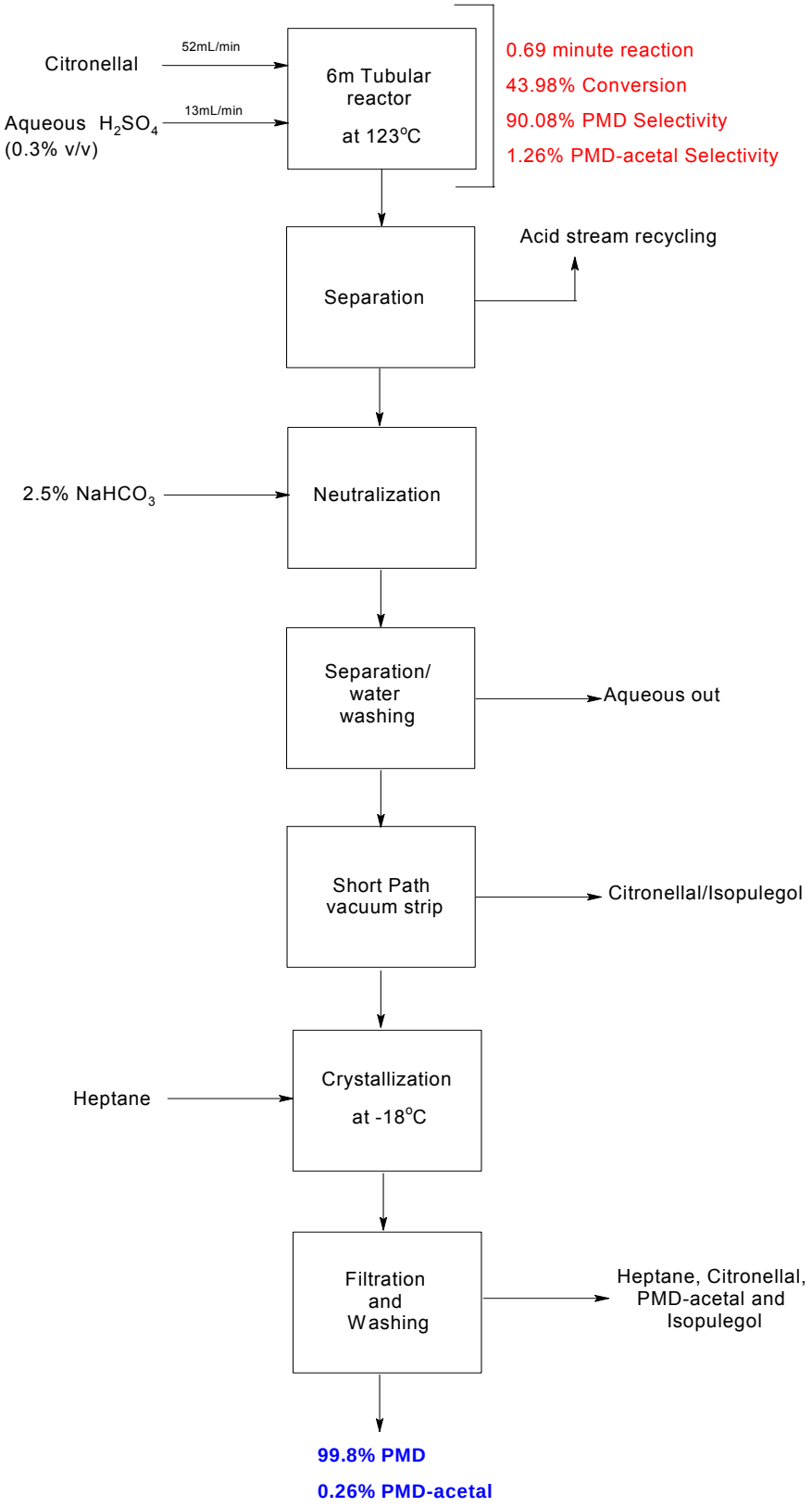


Diagram 6.1: Process flow diagram for the synthesis of PMD

The following table shows a comparison between the batch and SPP processes as developed during this study and published details of an industrial-scale batch process as operated by Takasago Japan.

Table 6.1: Comparison of the Takasago, Innoventon Batch and Innoventon SPP processes

Feature	Takasago	INNOVENTON Batch	INNOVENTON SPP
Mode of operation	Semi-Batch (Raw material added slowly to the catalyst phase over a period of 1 hour)	True batch (Material added in one step to the catalyst phase)	Continuous addition of organic and aqueous phases
Catalyst	Aqueous H_2SO_4 0.25wt %	0.3% H_2SO_4	0.3% H_2SO_4
Organic:Aqueous Ratio	1:3.7	1:4	1:4
Reaction temperature	55^{o}C	85 ^{o}C	123 ^{o}C
Substrate conversion	97.9%.	82%	43.98%
***p*-Menthane-3,8-diol selectivity**	92.3%	93.02%	90.08%
Acetal Selectivity	2.7%	1.6%	1.26%
Reaction period	11 hours (including reagent addition time)	7 min	0.69 min
Product isolation and purification	Vacuum distillation used for isolation. n-Heptane used for purification at -50^{0}C, for 20 hours. 80% yield obtained	Short path distillation used for isolation: n-heptane used for crystallisation purification at -18^{0}C, for 12hrs. 86% yield obtained	Short path distillation used for isolation: n-heptane used for crystallisation purification at -18^{0}C, for 12hrs. 86% yield obtained

It can be seen that the continuous process evaluated and developed during this study shows superior performance to both the comparative batch processes in terms of

productivity and selectivity. Using the concept of a Small Production Platform (SPP) has the following advantages:

- The continuous process allows for the production of PMD in a continuous manner which eliminates the variance commonly observed between batches and therefore produces a more stable output.
- The use of the SPP allows for the successive scale up of the PMD process using the numbering-up concept instead of the successive increase of reactor volumes to meet production capacities. This allows for instant process modifications to meet capacities which are not readily achieved by conventional equipment.
- The reaction can be performed above the boiling point of the aqueous phase at elevated pressures, which cannot readily be achieved by conventional batch equipment without modifications and reduction in process safety.

The product purification steps were also simplified significantly in comparison to current industrial practice.

It should be clear to the reader that significant opportunity exists to improve the process performance as summarized in Diagram 6.1 and Table 6.1. Examples of such potential improvement areas include:

(i) Using wider diameter tubes to significantly increase production rates;
(ii) Improving the mixing efficiency inside the reactor tubes to increase mass transfer rates, hence throughput rates, by, for example, using purpose-designed internal structuring, using faster flow rates (linear flow velocity), using dispersing aids to improve mixing and mass transfer, using small amounts of an inert solvent to aid mixing, etc.;
(iii) Increasing the reaction temperature further if improved mixing is achieved to further increase throughput rates.

In conclusion, the results obtained during this study have clearly shown the feasibility of producing PMD from citronellal by means of an acid-catalysed cyclization reaction by using a continuous process and using the concept of a Small Production Platform as defined in this work. The results of the work have been filed as a provisional RSA Patent Specification[1], and the University concluded a substantial Technology Transfer Agreement during July 2008 which will see full commercialization of the SPP-based continuous PMD process at the beginning of 2009 by the Pretoria-based company, Chemical Process Technologies PTY Ltd, in collaboration with an insect repellent manufacturing company, Afrepell PTY Ltd, and the NMMU (through InnoVenton). Lastly, the development and demonstration of the potential use of tubular reactors in a SPP concept opens the way for many similar developments.

6.6. References

1. G.M. Dugmore, S. Gouws, B. Mphulhu, I. Asquith, N. Rust, B.Zeelie, NMMU, A continous process for the synthesis of p-Menthane-3,8-diol, 2007.