Investigation of kinetics of a strongly exothermic reaction in microstructured reactors

Cyclisation of pseudoionone to $\beta$-ionone

Master project
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Abstract

Microstructured reactors (MSR) are innovative reactors with the dimensions in the submillimeter range along one or two axis, where chemical transformation takes place. MSR present heat transfer coefficients one order of magnitude higher than conventional reactors and heat exchangers, leading to process intensification. In the thesis, a commercially important, rapid and highly exothermic reaction, cyclisation of pseudoionone, is considered. Due to the high exothermicity, the reaction is conventionally carried out in a semi-batch wise manner which leads to a broad residence time distribution of the products making difficult to evaluate kinetics. Therefore, a microstructured system combining reactants in the form of droplets and allowing isothermal conditions and uniform residence time is used to study the kinetics. A reliable kinetic scheme is established describing the formation of the main product and by-products in parallel and consecutive reaction networks. Finally, the reaction conditions are optimised to increase yield and selectivity.
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Tables of symbols

<table>
<thead>
<tr>
<th>Reactor</th>
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<tbody>
<tr>
<td>(a)</td>
<td>Specific surface</td>
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<td>(d_t)</td>
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<td>(Q)</td>
<td>Reactants total flow rate</td>
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<td>Temperature</td>
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<td>(\tau)</td>
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<td>(E_a)</td>
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<td>(n(i))</td>
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<td>(\rho_i)</td>
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<td>(u)</td>
<td>Mean velocity</td>
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<td>(V)</td>
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<td>int</td>
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<td>MSR</td>
<td>Microstructured reactor</td>
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<td>RTD</td>
<td>Residence time distribution</td>
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1. Introduction

1.1. Microstructured reactors

1.1.1. Definition
Microstructured reactors (MSR) are defined as miniaturized systems whose characteristic internal dimensions typically range from the sub-micrometre to the sub-millimetre range [1]. Their fabrication has been possible through the advances in micro technology and precision engineering which have permitted the development of techniques such as micromachining, etching, electroforming, moulding and lithography. Besides MSR, the common microdevices are micro mixers, micro heat exchangers, micro separators, etc.

Several materials like glass, ceramic, metals and polymers are being used to develop the appropriate reactor, which depends on the reaction demand. Glass MSR, for example, is inert to a wide range of chemicals and in-situ optical measuring techniques can be integrated in it [2]. Polymers, however, have the particularity of being easy and inexpensive to fabricate compared to common processes used for ceramics [3]. Finally, stainless steel MSR have a good thermal conductivity (\( \lambda = 16.3 \) W/mK), which makes them very appropriate for exothermic reactions [4]. In Figure 1 four pictures for different MSR materials are shown.

![Figure 1: Different MSR materials a) glass, b) stainless steel, c) ceramic and d) polymer](image-url)
However, the importance of microstructured reactors relays on the several advantages they present over conventional reactors; not only in performance, but also in safety and costs. These advantages are mentioned in the following section.

1.1.2. **Fundamental advantages of microstructured reactors**

A large number of applications within the last decade clearly demonstrated fundamental advantages of miniaturized systems compared to conventional equipment. The most important ones are listed below:

- Enhanced mass and heat transfer
- High specific surface area
- Laminar velocity profile
- Narrow residence time distribution
- Mixing times in millisecond range
- Low hold-up, safety and control
- Scale-up by numbering-up
- Short response times

Some of them are explained with detail in the following paragraphs.

**Enhanced mass and heat transfer**

Volumetric mass transfer coefficient in MSR is in the range of \(1 \text{ s}^{-1}\) and heat removal capacity in the range of \(10^5 \text{ kW/m}^2\), exceeding those of conventional devices by at least one order of magnitude. This is due to decreasing linear dimensions, the gradient for a given physical property such as temperature or concentration increases, and so does its driving force. This important quality allows them to be the perfect tool to study fast and exothermic reactions.

In Figure 2, mass and heat transfer of conventional reactors is qualitatively compared with the one in MSR.
High specific surface area

If a circular cross section of a tubular reactor is assumed, the specific surface area is given by:

\[ a = \frac{\text{area}}{\text{volume}} = \frac{4}{d_i} \]  

Eq. 1

Considering that its diameter is in the sub-millimetre or sub-micrometre range, specific areas obtained can be up to 50,000 m\(^2\)/m\(^3\), which not only improves heat transfer but is also useful in catalytic gas and liquid phase reactors coated with active material on the inner walls.

Narrow residence time distribution

MSR have laminar flow, which is characterised by a parabolic velocity profile resulting in residence time distribution (RTD) along the length of the reactor. RTD depends on operating conditions such as characteristic dimension of the reactor (d\(_i\)), flow velocity and molecular diffusivity [6]. Considering the equation of axial dispersion and the dimensions of MSR, axial dispersion is reduced and laminar profile flattened, as shown in Figure 3.

\[ D_{ax} = D_m + \frac{u^2 \cdot d_i}{192 \cdot D_m} \]  

Eq. 2

Where \(D_{ax}\) is axial dispersion, \(D_m\) is molecular diffusion and \(u\) is the mean velocity.
Figure 3: Simulated concentration profiles in gas phase laminar flow for tubular reactors with different diameters
a) $d_t=20\text{mm}$, b) $d_t=2\text{mm}$ and c) $d_t=200\mu\text{m}$: ($\nu=10^{-5}\text{m}^2/\text{s}$, $D=10^{-9}\text{m}^2/\text{s}$, $Re=u_d/\nu=10$) [6]

However, as molecular diffusion for gas is higher than liquid phase ($10^{-5}\text{m}^2/\text{s}$ and $10^{-9}\text{m}^2/\text{s}$ respectively), narrow residence time distribution in liquid phase only occurs when residence time is considerably higher than radial diffusion time ($t_D$).

Mixing times in millisecond range
The high mixing in MSR can be explained by taking into account radial diffusion time of species present in it. When decreasing linear dimensions of a reactor to the micro range, radial diffusion time ($t_D \sim d_t^2/D_m$) decreases significantly.

Safety and control
The volume of MSR is significantly low (about a few micro liters) and so are the amounts of reactants needed resulting in enhanced safety. Besides, the well-defined flow regimes also help to control the operating conditions precisely.

Scale-up by numbering-up
Conventionally, the scale-up was done using the information obtained from lab-scale processes resulting in uncertainties in the design and hence the optimal performance of the process. However, by using microstructured reactors the large throughputs are obtained by numbering-up the reactor i.e. using multiple parallel units, so the transport properties remain unchanged. Besides, a larger number of parallel units result in higher production flexibility and a broader range of operating conditions compared with a macroscopic system.
1.2. Model reaction

In the present work, cyclisation of pseudoionone (PI) to β-ionone is considered as a model reaction. It is a commercially important reaction as the product is used in perfumery as well as in the synthesis of vitamin A.

As shown in Figure 4, the reaction has two steps, both of them catalysed by an acidic agent. The first step, known as cyclisation and where PI is transformed into α-ionone, is quasi-instantaneous and extremely exothermic ($\Delta H_r = -120$ kJ/mol); whereas the second step, known as isomerisation and where β-ionone is formed, is slower and slightly endothermic ($\Delta H_r = 8$ kJ/mol) [7].

Conventionally, the process is carried out in a semi-batch reactor containing a biphasic mixture of sulphuric acid and toluene. Given the fastness and the high exothermicity of the reaction, by-products can be formed. Therefore, efficient removal of heat and rapid quenching is needed. The slow dosing of PI allows a strict control of heat production, maintaining nearly isothermal conditions and avoiding thermal runaway. Extraction of ionones into organic phase occurs by adding water to the reaction mixture. Finally, toluene absorbs the reaction heat and also reduces the overall viscosity resulting in better mixing and higher heat transfer performance. The detailed literature review on influence of different solvents and operating conditions on the reaction is presented in Chapter 2.

1.3. Motivation and objectives

To investigate kinetics of such a reaction, the industrial process is not appropriate because of 1) mass transfer limitations due to biphasic system, 2) problems when interpreting data in semi-batch reactor caused by RTD and difficulties to maintain isothermal conditions, 3) the data is not accessible to low time scales. Some efforts have been made to eliminate the first two problems.
However, the industrial process is still not capable to access low time scales, demanding a new technique that fulfils this requirement but also avoids mass transfer limitations, residence time distribution and hot spot formation. This is possible in MSR.

An attempt has been made by Detraz [4] using a T-junction MSR and showed that the reaction (first step) was limited by mixing due to its quasi instantaneous nature. Besides, the residence time distribution in the laminar flow MSR proved to hinder the study.

Therefore, the main objective of this thesis is to overcome these limitations through a liquid-liquid fluid system combining two reactants in the form of slug which are carried by an inert carrier.

1.4. Outline of the thesis

In Chapter 2, a brief literature review summarising the most important solvents and operating conditions concerning the reaction is given. Further, in Chapter 3, an experimental set-up along with the operating conditions used in the present work is presented in detail. Chapter 4 contains the results and discussion on the flow patterns for the two-phase system, presenting the most suitable reactor material and flow rate conditions for the reaction to take place. The partitioning of different substances investigated is also presented. Moreover, concentrations profiles, conversion, selectivity and yield as well as apparent kinetics are quantified. Finally, conclusions and perspectives for future studies are given at the end of the thesis (Chapter 5).
2. State-of-the-art

In the past few decades, cyclisation of PI has been studied in different fluid systems, modes of operation and acidic agents. In this chapter, the state-of-the-art of this reaction is reported.

Cyclisation of PI was first studied in single-phase system by Smit et al. [8] and Semenovskii et al. [9]. They investigated the two steps of the reaction: cyclisation and isomerisation, carrying out a different set of experiments for each one. The starting mixture consisted of two PI isomers, sulphuric acid was used as the catalyst and nitromethane and nitropropane, both miscible with PI and sulphuric acid, were used as solvents. The operating temperatures were in the range of -40°C to 60°C and H$_2$SO$_4$:PI ratio varied from 0.4:1 to 11:1. The experimental results showed that the higher the H$_2$SO$_4$:PI ratio, the more β-ionone was formed, with a maximum yield of about 90%. Isomerisation experiments showed that by increasing reaction temperature, reaction time and sulphuric acid concentration, the yield of β-ionone also increased. Based on the observations, a reaction mechanism was proposed (Figure 5) and concluded that 1) overall reaction is independent of the initial isomer ratio of PI, 2) the reaction of PI to α-ionone is always accompanied by a parallel direct cyclisation of PI to β-ionone and 3) depending on the reaction conditions, α-ionone can be transformed into β-ionone.

![Figure 5: Mechanism proposed by Semenovskii et al. [9] for cyclisation of PI](image-url)
The outcome of this work led several authors to investigate not only the influence of acidic agents in the reaction, as they play an important role in the composition of ionones, but also operation modes and fluid systems (single-phase and two-phase). The most important ones are mentioned in the following sections.

2.1. Influence of acidic agents

Royals [10], after experimentation with several acids in a semi-batch reactor and through a two-phase system, concluded that composition of ionones could be estimated from the refractive index and an empirical correlation, (Eq. 3) in which percentage of β-ionone was dependant on the strength of the acid used:

\[
\% \beta\text{-ionone} = 15 \cdot \log aK + 87.7
\]

Karshan et al. [11] conducted some experiments with sulphuric (92%), phosphoric (85%) and toluenesulfonic acid (pure). The maximum yield obtained was about 97% for an ionone mixture mostly with α-ionone. The ratio acid:PI was varied from 0.025:1 to 0.2:1 and the operating temperatures from 70°C to 175°C. Further, an attempt to avoid sulphuric acid was made by Panfilov et al. [12], given the corrosion problems in the equipment and the handling difficulties when used in large amounts. They experimented with anhydrous hydrofluoric acid (HF) and obtained a maximum yield of β-ionone of about 91%. The ratio HF:PI was varied from 1:6 to 1:11 and the operating temperatures from -2°C to 10°C.

Markovich et al. [13] tried also to reduce the sulphuric acid amount by combining it with trifluoroacetic acid, which can be easily reused, and by mixing fluorosulphuric acid with also trifluoroacetic acid. As a consequence, H₂SO₄:PI ratio decreased drastically to 1.25:1.

Solid acid catalysts, such as synthesized macroreticular polystyrene resins, were used by Lin and Zhao [14] for the cyclisation of PI. The studies were carried out in a batch, with cyclohexane as solvent and at a temperature of 80°C. With 0.1g of catalyst, conversions in the range of 75% to 100% and selectivities to α-ionone from 5% to 25% were obtained. The formation of β-ionone was not observed. A maximum yield of 49% was afterwards obtained for Nafion NR50 and Amberlyst 36.
Although other solid catalysts were also studied by Lin et al. [15] and Guo et al. [16], the selectivity was very low. Recently, Diez et al. [17] obtained selectivities up to 79% with a HPA/SiO$_2$ catalyst and aprotic solvents. However, through several studies, a slight deactivation of HPA/SiO$_2$ was found out. Catalyst activity and ionone distribution proved to be highly dependent on HPA loading, reaction time, conversion level, reaction temperature and solvent, therefore needing further optimisations.

2.2. Continuous processes for cyclisation

In order to transform the batch or semi-batch processes in continuous mode, which have several advantages such as lower costs and reproducibility of product quality, some experiments are reported in the literature.

The first continuous process for cyclisation of PI were developed by Hertel et al. [18] in two different systems: a packed bed reactor and a thin film evaporator. The operating temperatures were in the range of 41°C to 61°C and concentrated sulphuric acid was used as a catalyst for the reaction. The solvent employed was CH$_2$Cl$_2$ (in the latter, solvents such as CHCl$_3$, CCl$_4$, hexane and pentane were also used) and quenching was achieved through hydrolysis of sulphuric acid with water. It was proved that β-ionone was predominant for H$_2$SO$_4$:PI ratio from 5:1 to 15:1 and maximum yield obtained was about 90%.

Further, Rheude et al. [19] developed another process with broader temperature and residence time ranges varying from 20°C to 90°C and from 0.5s to 2.5s. Concentrated sulphuric acid was used as a catalyst and for quenching, water or diluted sulphuric acid were employed. It was concluded that α-ionone was the main product for H$_2$SO$_4$:PI ratios 2:1 and 3:1 whereas β-ionone was preferred for H$_2$SO$_4$:PI ratio higher than 5:1. This process is schematically presented in Figure 6.
Finally, Dobler et al. [20] developed a continuous process with sulphuric acid (50-90%) and an inert diluent. For optimised conditions (acid concentration <90%, T<20°C and residence time>10s), β-ionone was formed at high yields whereas α- and γ-ionones were extremely low (1%).

Microstructured reactors
Several studies in microstructured reactors were also carried out in order to overcome the mass and heat transfer limitations of the process, given the rapid and highly exothermic nature of the reaction.

Wörz et al. [21] developed a MSR based continuous process consisting of a mixer followed by a cooler for an identical reaction system. Hexane was used as solvent and concentrated sulphuric acid as catalyst, thus forming a two-phase system. The residence times were varied from 0.2s to 4s. As initially a hot spot of 35K was observed in micromixing zone, a new system consisting of 32 stainless steel channels (900µm x 60µm) separated by cooling channels was built by Institut für Mikrotechnik Mainz (IMM) and BASF AG. Through this system hot spot was reduced to 1K and yield of about 85% was achieved at 50°C and 4s residence time. Given the high exothermicity of the quenching step, that took place in the micromixer, proving the reduction of by-products by half.

Finally, Dessimoz [22] carried out the reaction in a T-junction and through a two-phase system: sulphuric acid and toluene (solvent). The author characterised flow patterns, concluding that parallel flow was observed in the range of 10 ml/h to 120 ml/h. The results also showed that
reaction took place in aqueous phase and that products were extracted from acid phase to toluene by water addition. Conversion achieved was between 80% and 90% and yield of \( \beta \)-ionone was in the range of 50% to 60%.

### 2.3. Differences between single-phase and two-phase system

In order to study the differences between single-phase system and conventional two-phase system (toluene as solvent and sulphuric acid as catalyst), Kashid et al. [7] carried out experiments in batch and semi-batch using two different solvents: toluene and nitropropane.

**Studies with toluene: two-phase system**

The experiments were carried out in a stirred glass reactor in a semi-batch mode, with a dosing time of PI about 45 min. The mixture of sulphuric acid and toluene was cooled to -10 °C and PI was dosed slowly. The ratio PI:H\(_2\)SO\(_4\) was varied from 1:1.2 to 1:4.8.

Experimental results proved that the reaction was taking place in acidic phase and the products were extracted to organic phase upon of dilution of sulphuric acid to about 60wt%. It was also observed that 20% of the ionones were lost forming unidentified by-products. Besides, it was noted that diluted sulphuric acid led to a reduction of the overall yield.

**Studies with nitropropane: single-phase system**

After having tested different solvents, Kashid et al. [7] used 1-nitropropane as a solvent to overcome the mass transfer limitations occurring in two-phase system and to avoid direct contact of concentrated sulphuric acid with PI (while dosing) as well as with water (while extraction). It was found out that ionones yield was considerably higher (99%) compared to the two-phase system, while the \( \alpha \)- to \( \beta \)-ionone transformation rate was lower because of the dilution of sulphuric acid by nitropropane (\( \beta \)-ionone yield was about 89%).

Finally, when the experiments were carried out in a batch to investigate the reaction kinetics, it was observed that the transformation of PI to \( \alpha \)-ionone showed quasi-instantaneous behaviour while \( \alpha \)-ionone to \( \beta \)-ionone was found to be moderate step as shown in Figure 7.
2.4. Kinetics of cyclisation

Kashid et al. [7] investigated the kinetics of isomerisation step using batch reactor due to moderate rate of transformation. It was found out that transformation from α- to β-ionone was a first order reaction with activation energy close to 65 kJ/mol. However, no efforts had been made to investigate the kinetics of the PI to α-ionone transformation until Détraz [4] carried out experiments in a T-shaped microstructured reactor using a single-phase system proposed by Kashid [7].

Détraz [4] performed experiments in a MSR for a residence time range of 1 to 36 s. The set-up consisted of a stainless steel T-junction of 0.5 mm outlet diameter (Figure 8b), introduced in a cooling bath in order to maintain isothermal conditions. The concentration of PI was fixed to 0.4M and the acid:PI ratio to 1:11 (proved to be a ratio in which β-ionone was preferred) over a temperature range of 0°C to 50°C.
For the first time, an intermediate was observed and the reaction scheme was then proposed from the concentration behaviour of reactant, intermediate and products.

\[
\text{PI} \rightarrow \text{Intermediate} \rightarrow \beta\text{-ionone}
\]

However, while fitting experimental data with the model assuming first order behaviour of all steps, it was found out that activation energy of the reaction was not intrinsic (dependence on flow rate and temperature). It was then concluded that reaction was limited by mixing. Besides, the typical laminar flow profile gave residence time distribution in the system, leading to complexities in predicting accurate information. In addition to this, drops were formed at the outlet of the MSR before falling to the collecting flask, causing additional inaccuracy of residence time. Therefore, some modifications in the experimental system were required, which is the objective of the work presented here.
3. Experimental

The experimental work was divided in three parts: 1) flow regime characterisation, 2) partitioning of reactants and products and 3) cyclisation experiments. The main idea is to find out a well-defined slug flow regime and to carry out the reaction in it.

3.1. Experimental set-up

3.1.1. Microstructured reactor
The MSR consisted of a cross-junction (Figure 10) which acted as a mixer by contacting both reactants (Inlets 1 and 3). Given the organic character of both solvent (NP) and carrier (PFH), hydrophilic (glass) and hydrophobic (PTFE) materials were tested.

![Figure 10: cross-junction MSR](image)

3.1.2. Pumping system
Two pumps were used to push the flow into the system: a single syringe pump for continuous phase and a double syringe pump for dispersed phase. The second one, which accommodated two syringes, provided equal flow rate to the reacting species, which was very important given the different viscosities of them. Glass Hamilton syringes of 50 ml capacity were employed.

3.1.3. Capillary
The inlet capillary consisted of PTFE tubes of 0.8 mm internal diameter while the outlet tubes had a 0.5 mm internal diameter. External diameter of all of them was 1.58 mm.
3.1.4. Chemicals and solutions

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<td>For synthesis (Merck)</td>
</tr>
<tr>
<td>1-Nitropropane</td>
<td>For synthesis (Merck)</td>
</tr>
<tr>
<td>Perfluorohexane</td>
<td>For synthesis, 98% (Alfa Aesar)</td>
</tr>
<tr>
<td>Pseudoionone</td>
<td>2 isomers (Givaudan)</td>
</tr>
<tr>
<td>Sodium carbonate</td>
<td>For synthesis (Alfa Aesar)</td>
</tr>
<tr>
<td>Sudan III</td>
<td>For synthesis, (Sigma Aldrich)</td>
</tr>
<tr>
<td>Sulphuric acid</td>
<td>For synthesis, 95-97wt% (Merck)</td>
</tr>
</tbody>
</table>

The experimental set-up for flow regime characterisation is represented schematically in Figure 11. A pure NP solution and another with NP and sudan (red dye) were filled in the syringes referring to inlets 1 and 3, while a PFH solution was filled in the other syringe (for more precision of flow pattern, in some experiments pure NP was replaced by the sulphuric acid solution, see 4.1.4). The mixture at the outlet was collected in a volumetric flask. After having obtained pictures from the current flow regime through a camera (MotionPro X4) situated over the midway capillary, the system was stopped and flow rates for both pumps were changed to the new desired values. The programs used to edit the images captured were Motion pro 5.1 and ImageJ. Once the experiments were finished, PFH was separated from all other substances, being ready to be re-used.
As for partitioning, two sets of experiments were carried out: 1) mixing of pure PFH and NP 2) mixing of pure PFH with a PI solution. In the first set, four graduate cylinders were filled with NP: two of them with 4 ml and the other two with 2.4 ml. Further, 4 ml of PFH were added to the first and 6 ml to the second. The mixtures were stirred for approximately 1 minute. Finally, 2 of the graduate cylinders with 4 ml and 2.4 ml of NP, respectively, were kept in the fridge for about 2 hours while others were kept at room temperature for about the same time. The change of volume of PFH was noted and percentage of NP transferred was quantified. In the second set of experiments, NP was replaced by PI solution. PI solution was separated from PFH and analysed with gas chromatography (GC). Thus from the difference of initial and final concentration, the amount of PI transferred to PFH was quantified.

For cyclisation, experiments were carried out with the same experimental set-up, as represented schematically in Figure 12. The PTFE cross-junction, found to be the most suitable in flow regime experiments, the outlet capillary and part of inlet capillaries were immersed in a thermal bath (Vₜ=0.23 l) filled with ethylene glycol. The temperature in the system was controlled by thermostat Huber CC3. Reacting species (PI and H₂SO₄ solutions) and carrier were filled in the corresponding syringes. After a few minutes during which the system had reached the steady state, a conical flask with 40 ml of distillate water together with about 5 g of sodium carbonate and a magnetic stirrer was positioned according to Figure 12, with an ice bath surrounding it. This caused the dilution of sulphuric acid in the aqueous phase and the quenching of the reaction. Two different samples were collected for each temperature, for the
collecting time 15 min for each one. The two phases were allowed to separate and organic phase was withdrawn. Samples were then dried with 3 g of sodium carbonate and analysed through GC. For blank experiments an identical procedure was used with the sulphuric acid replaced by pure NP. When experiments were finished, the system was first cleaned with ethanol, in order to remove sulphuric acid from the capillary walls, and after with hexane, in order to eliminate PFH.

Figure 12: Experimental set-up for cyclisation experiments

GC analysis
In order to perform GC analysis, the following amounts of substances were introduced into a GC vial:

- 200 µl of PI sample
- 120 µl of 2%wt butanol in ethanol solution
- 450 µl of pure nitropropane

Concentrations of all species present in the sample were quantified from the peak areas in the GC spectrum.
3.2. Operating conditions

The overall operating conditions of all experiments are reported in Table 3.

Table 3: Operating conditions of flow regime characterisation, partitioning and cyclisation

<table>
<thead>
<tr>
<th>OPERATING CONDITIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Flow regime characterisation</strong></td>
</tr>
<tr>
<td>Cross-junction</td>
</tr>
<tr>
<td>Temperature</td>
</tr>
</tbody>
</table>
| Flow rate             | PFH: 1-8 ml/min  
                        | NP (total): 0.2-6 ml/min |
| Outlet capillary      | 0.5 mm internal diameter  
                        | 40 cm length |
| **Partitioning**      |
| Temperature           | 0ºC and 25ºC |
| Graduate cylinders    | 10 ml      |
| Sealed glass flasks   | 20 ml      |
| Volumetric PFH:NP/PI ratios | 1:1 and 2.5:1 |
| **Cyclisation**       |
| Temperature           | -20ºC to 10ºC |
| Cross-junction        | PTFE       |
| Flow rate             | PFH: 1 ml/min  
                        | PI and H₂SO₄ (total): 0.4 ml/min |
| Outlet capillary length | 10-40 cm  |
| Residence time        | 0.84-3.32 s |
| H₂SO₄:PI ratio        | 1:10       |
| Concentrations        | PI solution: 0.4 M  
                        | H₂SO₄ solution: 4 M |

For flow regime characterisation, the operating temperature was 25ºC and the tested flow rates were 1-8 ml/min for PFH and 0.2-6 ml/min for NP (inlets 1 and 3).

Partitioning experiments were carried out at two temperatures: 0ºC and 25ºC and at two volumetric PFH: NP/PI ratios: 1:1 and 2.5:1. This last ratio was tested because in cyclisation experiments, the flow ratio of carrier:reactants was 2.5:1.

In cyclisation experiments operating temperature was in the range of -20ºC to 10ºC. The operating flow rate was 1 ml/min for PFH and 0.4 ml/min for both reactants, given that it was found to be the most suitable flow conditions for the reaction, and it was maintained constant to
preserve flow pattern and mixing within drops. Therefore, in order to work with different residence times, the outlet capillary length was varied from 10 to 40 cm. Concentrations of PI and sulphuric acid with NP as a solvent were fixed to 0.4 M and 4 M respectively (PI:H$_2$SO$_4$ ratio was 1:10).
4. Results and discussion

4.1. Flow regime characterisation

4.1.1. Two-phase flow pattern

Understanding and modelling two phase flows in microchannels, such as the fluid system of the current study, is a topic of considerable interest, not only in the field of chemical engineering but also in biomedics and pharmaceutical science for example. There are already several authors who have focused on gas-liquid and liquid-liquid flow pattern, being the purpose of these studies the prediction of flow behaviour under various operating conditions.

Channel size, phase superficial velocities, liquid phase surface tension and channel wettability are found to be the most significant parameters affecting flow configurations in gas-liquid systems. It is also postulated that 6 different flow regimes can be observed in such systems: bubbly and Taylor flows (surface tension dominated), transitional churn, Taylor-annular flow and dispersed and annular flows (inertia dominated) [23].

As for liquid-liquid systems, flow patterns are not well understood. A number of studies have been done in order to characterise different flow regimes and to attain slugs to carry out and enhance two-phase chemical reactions [24]. In such reactions, the dispersed phase, which contains reaction mixture and allows uniform residence time, is mixed through internal circulations, as shown in Figure 13. Considering the advantages which this configuration presents, the aim of this study is to investigate kinetics of cyclisation using such a system.

![Figure 13: Scheme of reaction system](image)

[Figure 13: Scheme of reaction system]
According to this scheme, an immiscible and non-reactive carrier is needed. After having studied various solvents such as hexane, cyclohexane, heptane, acetonitrile, toluene and perfluorohexane, only the latter was found out to fulfil the requirements mentioned.

In order to characterise flow pattern of the two-phase system, due to the high exothermicity of the reaction, only the solvent-carrier system was tested. The prerequisites were:
   1) NP slug flow (continuous phase has backmixing)
   2) Regular slugs
   3) Good mixing of two NP inlets

The red dye in one inlet was used in order to determine mixing qualitatively.

Moreover, considering that both PFH and NP were organic compounds and it was very difficult to predict dispersed and continuous phase a priori, two materials with different wetting properties were tested:
   - Glass: hydrophilic
   - PTFE: hydrophobic

In the following sections, results for both materials are presented.

4.1.2. Glass reactor

For glass reactor, two different flow regimes were identified in the case where PFH was initially saturated with NP:
   - PFH slug flow
   - Parallel flow

The snapshots of different flow configurations are shown in Figure 14.

Figure 14: Flow configurations in glass MSR a) PFH slug flow (NP flow rate: 0.06 ml/min, PFH flow rate: 0.06 ml/min) and b) Parallel flow (NP flow rate: 1 ml/min, PFH flow rate: 2 ml/min)
It is observed that in parallel flow NP stays on the walls while PFH flows in the inner part of the capillary.

The results obtained for glass MSR are presented in Figure 15. As it is shown in Figure 15a, for all experiments between 1-8 ml/min of PFH and 0.2-6 ml/min of NP parallel flow is the only regime observed. Therefore lower flow rates of both fluids were also studied. According to Figure 15b slug flow takes place in the whole range of NP flow rates, only when PFH flow rate is low enough (0.06 to 0.1 ml/min). A dashed line shows the approximate boundaries of each flow configuration.

These results clearly show that in glass, which is a hydrophilic material, NP flow is in the form of continuous phase while PFH is the dispersed phase. Therefore, the material does not fulfil the first requirement of NP as dispersed phase and it is found to be not suitable to carry out the reaction.

4.1.3. PTFE reactor
For PTFE reactor, three different flow regimes were identified in the case where PFH was initially saturated with NP:

- NP slug flow
- Parallel flow
- Transition flow
This last configuration was called transition flow because it shifted randomly from slug flow to parallel flow and vice versa.

The snapshots of the 3 flow regimes are shown in Figure 16.

![Image](image1)

**Figure 16**: Flow configurations in PTFE MSR a) Slug flow (NP flow rate: 0.6 ml/min, PFH flow rate: 1 ml/min), b) Parallel flow (NP flow rate: 2 ml/min, PFH flow rate: 2 ml/min), c) Slug flow in transition flow (NP flow rate: 0.8 ml/min, PFH flow rate: 1 ml/min) and d) Parallel flow in transition flow (NP flow rate: 0.8 ml/min, PFH flow rate: 1 ml/min)

In the parallel/annular flow, PFH stays on the walls while NP flows in the inner part of the tube.

A flow map has been established from these different configurations, in which PFH flow rate is varied from 1 to 8 ml/min while NP flow rate range goes from 0.2 to 6 ml/min.
As it is shown in the figure, slug flow occurs in the whole range of PFH flow rates, only when NP flow rate is low enough (0.2 to 0.6 ml/min). However, as soon as the latter increases, so does instability of slugs, arriving at a transition regime. Finally, for NP flow rates higher than 2 ml/min, parallel flow is observed, irrespective of the value of PFH flow rate. It is concluded then, that NP is the limiting flow rate when forming slug-flow. Dashed lines show the transition boundaries of the flow regimes.

These results clearly show that PTFE, which is a hydrophobic material, gives NP as a dispersed phase while PFH is the continuous phase. Therefore, the material fulfils the first requirement mentioned in 4.1.1.

The slug length and standard deviation size is shown in Figure 18.
As it is seen from the graph, (0.2,1) and (0.6,4) are the flow rate conditions in which slugs are found to be more regular (lowest standard deviation).

The third requirement is the mixing of two reactants in drops. It was observed in all experiments that the two NP inlets were perfectly mixed because the outlet was homogeneously coloured in pale red (the mixture of red colour and transparent).

Therefore, PTFE was found out to be a suitable material to carry out the reaction, with the rates of (0.2,1) and (0.6,4) showing regular slugs.

4.1.4. Reactor of choice

From the results discussed in the previous sections, it is clear that PTFE is the only choice to carry out the reaction in a liquid-liquid slug flow environment. As it was explained in 4.1.1, in order to characterise flow regime, the system NP-PFH was studied. Nevertheless, two more chemicals dissolved in NP are also involved in the reaction: PI and sulphuric acid. Both of them have a higher viscosity than NP (Table 4) which is likely to modify flow regime.
### Table 4: Viscosity of chemicals used in cyclisation experiments

<table>
<thead>
<tr>
<th>Chemical</th>
<th>μ (T=20°C) (cP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Nitropropane</td>
<td>0.844</td>
</tr>
<tr>
<td>PI</td>
<td>5.71</td>
</tr>
<tr>
<td>Sulphuric acid</td>
<td>26.7</td>
</tr>
</tbody>
</table>

Considering that concentrations of PI and sulphuric acid solutions needed for the reaction are 0.4 M and 4 M respectively, it is possible to neglect the effect of viscosity of PI but not of the sulphuric acid, given both high viscosity and high concentration of the substance. Therefore, several experiments using sulphuric acid solution of 4 M, which substituted the uncoloured NP inlet, were performed. The results showed that the most suitable flow rate for the two inlets containing reaction mixture was 0.4 ml/min and for the carrier inlet 1 ml/min, because of the good mixing of the NP and sulphuric acid inlets and the mostly regular slug-flow observed.

This flow rate was fixed for the further experiments on kinetics of cyclisation.

### 4.2. Partitioning

#### 4.2.1. Mass transfer

When considering two-phase systems, not only flow pattern characterisation is needed, but also partitioning or solubility of one species into another. The mass transfer takes place from the phase with higher chemical potential into the other until the equilibrium is reached [25]. At that time, concentration of a component (i) in each phase is known as equilibrium concentration and the ratio between both concentrations is called as partition coefficient. However, at higher concentrations, one of the phases gets saturated with the component and then it is called as saturation zone.

![Mass transfer of a compound from one phase to the other](image)

**Figure 19: Mass transfer of a compound from one phase to the other**

In the present work, the homogeneous reaction takes place inside the slug in liquid-liquid environment, so the mass transfer of reaction species in the carrier (perfluorohexane) needs to
be quantified (diffusion of sulphuric acid into the carrier is not considered given its inorganic nature), in order to have a precise estimation of kinetic parameters.

4.2.2. Experimental results

In this section mass transfer of NP, PFH and ionones has been estimated. Two sets of experiments were carried out: partitioning of NP and PI. Two operating temperatures (0°C and 25°C) were chosen in order to see the effect of solubility with temperature. Volumetric ratio between two phases (NP:PFH) was also variable with conditions of 1:1 and 1:2.5.

In the first set of experiments pure PFH and NP solutions were mixed intensively in a cylinder and kept for some time to separate. The goal was to determine the amount of NP which had diffused in the PFH solution. The results for the changes of volume for two phases are reported in Table 5.

As expected, at higher temperature, higher NP amount diffuses into PFH. This is due to the fact that solubility increases with temperature. The results were not affected by volumetric ratio, as PFH was saturated with NP. Through equations 4 and 5, wt% of NP in PFH and % mass transfer of NP were quantified (Table 6).

\[
\text{wt% NP in PFH} = \frac{\Delta V \cdot \rho_{NP}}{V_0 \cdot \rho_{PFH} + \Delta V \cdot \rho_{NP}} \cdot 100 \quad \text{Eq. 4}
\]

\[
\%NP \text{ transferred} = \frac{\Delta V}{V_{tot} - V_0} \cdot 100 \quad \text{Eq. 5}
\]
Where: \( \rho_{PFH} = 1710 \text{ kg/m}^3 \) and \( \rho_{NP} = 990 \text{ kg/m}^3 \)

<table>
<thead>
<tr>
<th>T (°C)</th>
<th>wt% NP in PFH</th>
<th>% NP transferred</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>3.26%</td>
<td>10.8%</td>
</tr>
<tr>
<td>0</td>
<td>2.12%</td>
<td>7.5%</td>
</tr>
</tbody>
</table>

From this table it is observed that the diffused nitropropane represents about 3.3% (57.7 g NP/l PFH) maximum of the PFH phase when temperature is 25°C. This value is low enough to be neglected from PFH phase. On the other hand, the maximum NP transferred compared to the initial solution represents ~11%, which is much more significant. Nevertheless, in the kinetic experiments the sample was collected at 0°C so the percentage of NP transferred was ~7.5%, resulting in slight discrepancies in mass balances of the experimental results. The solubility of NP in PFH at that temperature was found to be about 37g/l.

In the second set of experiments, saturated PFH and PI in NP were mixed. The PI was analysed after separation in GC. The difference in amount gave the PI transferred in PFH. The operating temperature was fixed to 0°C. Two experiments were performed for identical conditions in order to check the reproducibility. Initial and final PI concentrations (Eq. 6) and %PI transferred to PFH are reported in Table 7.

\[
\% \text{ mass transfer PI} = \frac{n(\text{PI})_{\text{fin}} - n(\text{PI})_{\text{in}}}{n(\text{PI})_{\text{in}}} \times 100
\]

Eq. 6

Where \( n(i) \) represents the number of moles of species \( i \)

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>PFH:PI ratio</th>
<th>( C(\text{PI})_0 ) (M)</th>
<th>Average ( C(\text{PI})_F ) (M)</th>
<th>% transferred PI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1:1</td>
<td>0.257</td>
<td>0.342</td>
<td>0.00154%</td>
</tr>
<tr>
<td>0</td>
<td>1:2.5</td>
<td>0.257</td>
<td>0.387</td>
<td>0.00127%</td>
</tr>
</tbody>
</table>

The results are in agreement with the ones for NP in Table 6, because the more NP transfers to PFH, more concentrated is the PI solution. It is also observed that given this increase in concentration, the amount of PI which transfers to PFH is significantly lower than NP.
From these results it is observed that PI transferred represents a very low percentage of initial solution. Since all ionones have identical chemical properties, mass transfer of ionones can also be neglected. Besides, a PFH sample which had been in contact with reaction mixture was analysed in the GC. The GC spectrum is presented in Figure 21.

![Retention times](image)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Retention time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitropropane</td>
<td>2.1</td>
</tr>
<tr>
<td>α-ionone</td>
<td>5.7</td>
</tr>
<tr>
<td>β-ionone</td>
<td>6.5</td>
</tr>
</tbody>
</table>

**Figure 21: Analysis of perfluorohexane in GC**

From the overall results, it can be concluded that NP is partially miscible with PFH (37.9 g/l at 0°C) affecting mass balance calculations and that PI and ionones have negligible solubility in the carrier.

### 4.3. Cyclisation studies

After carrying out preliminary experiments such as flow regime characterisation and partitioning, the experiments of cyclisation, which are the main objective of the thesis, were conducted.

As it is mentioned in state-of-the-art, cyclisation reaction has been studied with detail in the past few decades. The first step of the reaction (cyclisation) is quasi instantaneous while the second step (isomerisation) is moderate. Intrinsic kinetics of isomerisation were studied in a batch and the reaction was found to be first order with activation energy about 65 kJ/mol. The Arrhenius plot shown in Figure 22 was obtained by data fitting for different temperatures.
As it is seen from the graph, different rate constants were obtained for α-ionone transformation and β-ionone formation, indicating a two step reaction. The hypothesis of an intermediate was therefore postulated.

Concerning the first step, mass transfer limitations lead to apparent kinetics when studied in T-junction micro reactor [4]. Nevertheless, the lower time scales possible in MSRs allowed to access to an intermediate. Detraz [4] thought that the intermediate was identical to that of isomerisation and the following reaction scheme was proposed.

\[
\text{PI} \\
\downarrow \\
\alpha\text{-ionone} \rightleftharpoons \text{Intermediate} \rightarrow \beta\text{-ionone}
\]

Taking this information as a starting point, the new results are discussed in further sections.

### 4.3.1. Preliminary experiments

As mentioned in experimental part, reaction was carried out in a PTFE cross junction MSR, consisting of 3 inlets and one outlet according to Figure 24.
Initial concentration of PI solution was fixed to 0.4 M, given that previous studies with lower concentrations showed higher discrepancies in mass balances. Initial concentration of sulphuric acid was consequently fixed to 4 M, in order to maintain a PI:H$_2$SO$_4$ ratio of 1:10, which promotes β-ionone formation (see Chapter 2).

Reactants and carrier were introduced in the system through two syringe pumps. One of the pumps is able to work with two syringes simultaneously, which allowed the injection of PI and sulphuric acid solutions at the same flow rate: 0.2 ml/min. The flow rate of the single syringe pump, which contained perfluorohexane, was set to 1 ml/min. These conditions were found to be the most suitable ones for the reaction in discussion of section 4.1.4.

Experiments were carried out at three different residence or reaction times: 0.84, 1.68 and 3.32 s. By changing the outlet capillary length and maintaining flow rates of all solutions constant, flow pattern and mixing conditions remained unchanged.

Reaction mixture was collected at the outlet for about 15 min and quenched with water and Na$_2$CO$_3$. An ice bath surrounding the conical flask permitted to maintain at a temperature of 0°C at the outlet. During quenching step, H$_2$SO$_4$ is transferred to the aqueous phase. The organic phase was analysed with gas chromatography.

4.3.2. Analytical results
In this section, the typical analytical results obtained are compared with the present results in Figure 25. In T-junction experiments, PI, ionones and an intermediate were identified (Figure
25c). However, in cross-junction, apart from the species present in T-junction studies, two additional peaks were observed in between α- and β-ionones (figure 25d). This happened because though Detraz [4] mentioned working with low residence times, due to drop formation time at the outlet of the capillary, residence time estimated was not precise.

By decreasing both reaction time and temperature, peak areas increased and in some cases overlapped, constituting a single peak. In order to assess that the compound was part of the reaction and not an impurity, residue or side product, an analysis of PI solution was performed also with a blank experiment. The blank experiment consisted of injecting a mixture of PI on one side of the reactor and pure nitropropane on the other, without sulphuric acid. The results from both analysis are shown in figures 25a and b.
Figure 25: GC spectrum of a) initial PI solution, b) blank experiment, c) cyclisation in T-junction and d) cyclisation in cross-junction.
Table 8: GC retention times of species involved in the reaction

<table>
<thead>
<tr>
<th>Substance</th>
<th>Comments</th>
<th>Retention time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudoionone</td>
<td>Givaudan</td>
<td>7.6</td>
</tr>
<tr>
<td>α-ionone</td>
<td>Product</td>
<td>5.7</td>
</tr>
<tr>
<td>β-ionone</td>
<td>Product</td>
<td>6.5</td>
</tr>
<tr>
<td>Intermediate 1</td>
<td>T-junction exp</td>
<td>13.4</td>
</tr>
<tr>
<td>Intermediate 2</td>
<td>Cross-junction exp</td>
<td>6</td>
</tr>
</tbody>
</table>

As shown, the additional peak indicated did neither appear in initial PI solution nor in blank experiment analysis. Besides, by following the evolution of its concentration as a function of reaction time, the typical behaviour of an intermediate was observed.

Concluding, two intermediates have been found in the reaction: intermediate 1, identified in T-junction studies, and intermediate 2, discovered through experiments in cross-junction; the latter shows a very close chemistry to both ionones, given the proximity of its peak to the α- and β-ionone peaks.

4.3.3. Model and fitting

After the information obtained from GC analysis, explained with detail in previous section, and the kinetic scheme proposed by Détraz [4] (Figure 23), a modified kinetic scheme (Figures 26 and 27) is suggested:

![Modified kinetic mechanism for cyclisation of PI](image)

In Figure 27, the species shown in the brackets are intermediates thought to be formed. However, the species found in GC should look different as they are formed after addition of water to reaction mixture.
As observed, intermediate 2 has been introduced in the isomerisation step, given its close chemistry (closed ring configuration) compared to ionones.

In order to fit experimental data to the proposed kinetic scheme, steps 1 and 2 have been assumed as pseudo-first order. Besides, isomerisation is known as a first order reaction.

Equations of the model are reported below:

\[
\frac{dC(PI)}{dt} = -k_1 \cdot C(PI) \quad \text{Eq. 7}
\]

\[
\frac{dC(int1)}{dt} = k_1 \cdot C(PI) - k_2 \cdot C(int1) \quad \text{Eq. 8}
\]

\[
\frac{dC(int2)}{dt} = k_2 \cdot C(int1) - k_3 \cdot C(int2) + k_4 \cdot C(\alpha) - k_5 \cdot C(int2) \quad \text{Eq. 9}
\]

\[
\frac{dC(\alpha)}{dt} = k_3 \cdot C(int2) - k_4 \cdot C(\alpha) \quad \text{Eq. 10}
\]

\[
\frac{dC(\beta)}{dt} = k_5 \cdot C(int2) \quad \text{Eq. 11}
\]
Table 9 shows the experimental data used for the fitting at a temperature of 0°C. Experiments were carried out at least twice, in order to check reproducibility and achieve more precision in the fitting.

<table>
<thead>
<tr>
<th>$\tau$(s)</th>
<th>C(PI) (-)</th>
<th>C(α) (-)</th>
<th>C(β) (-)</th>
<th>C(int1) (-)</th>
<th>C(int2) (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.84</td>
<td>0.371</td>
<td>0.217</td>
<td>0.050</td>
<td>0.425</td>
<td>0.020</td>
</tr>
<tr>
<td>0.84</td>
<td>0.317</td>
<td>0.217</td>
<td>0.050</td>
<td>0.436</td>
<td>0.021</td>
</tr>
<tr>
<td>1.68</td>
<td>0.031</td>
<td>0.442</td>
<td>0.100</td>
<td>0.338</td>
<td>0.061</td>
</tr>
<tr>
<td>1.68</td>
<td>0.038</td>
<td>0.496</td>
<td>0.113</td>
<td>0.369</td>
<td>0.190</td>
</tr>
<tr>
<td>3.32</td>
<td>0.007</td>
<td>0.705</td>
<td>0.125</td>
<td>0.089</td>
<td>0.026</td>
</tr>
<tr>
<td>3.32</td>
<td>0.006</td>
<td>0.702</td>
<td>0.153</td>
<td>0.061</td>
<td>0.029</td>
</tr>
<tr>
<td>3.32</td>
<td>0.009</td>
<td>0.616</td>
<td>0.109</td>
<td>0.182</td>
<td>0.037</td>
</tr>
</tbody>
</table>

The normalised concentration is defined as:

\[
\text{Normalised concentration (i) } = \frac{C(i)}{C(PI)_{\text{inlet}}} \tag{12}
\]

The experimental results were introduced in Berkeley Madonna program in order to obtain the reaction rate constants of all steps. At first, through equation 7 and PI normalised concentration at different reaction times, $k_1$ was obtained and fixed for further calculations. Secondly, through equation 8 and normalised concentrations of both PI and intermediate 1, reaction rate constant $k_2$ was determined and fixed. Finally, $k_3$, $k_4$ and $k_5$ were obtained by taking into account normalised concentrations of all species and equations 9, 10 and 11.

Figure 28 shows the normalised concentration profiles of all species, as a function of reaction time, with both experimental data and fitting from the model.
As can be seen from the figure, experimental data is in agreement with the model. The pseudo-first order assumptions of first and second steps are therefore correct.

Graphs with the experimental data and model fitting curves at temperatures of 10°C, -10°C and -20°C can be found in the appendix.

**4.3.4. Arrhenius plots**

In order to determine activation energy of all steps, rate constants obtained from the model at four different temperatures were determined (Table 10) and plotted in form of Arrhenius plot (Figure 29). Isothermal conditions were obtained through a constant temperature bath in which the cross-junction reactor was immersed.
Table 10: Rate constants obtained from the model at 4 different temperatures

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>$k_1$ (s$^{-1}$)</th>
<th>$k_2$ (s$^{-1}$)</th>
<th>$k_3$ (s$^{-1}$)</th>
<th>$k_4$ (s$^{-1}$)</th>
<th>$k_5$ (s$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-20</td>
<td>1.17</td>
<td>0.507</td>
<td>6.66</td>
<td>0.0371</td>
<td>0.841</td>
</tr>
<tr>
<td>-10</td>
<td></td>
<td>0.630</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1.41</td>
<td>0.919</td>
<td>12.9</td>
<td>0.822</td>
<td>1.08</td>
</tr>
<tr>
<td>10</td>
<td>1.82</td>
<td>1.08</td>
<td>31.7</td>
<td>2.18</td>
<td>2.61</td>
</tr>
</tbody>
</table>

As pointed out before, the rate constant increases with temperature with high increase in the rate $k_4$ followed by $k_3$.

Arrhenius law is given by:

$$
\ln k = \ln k_0 - \frac{E_a}{R \cdot T}
$$

Eq. 13

Where $k_0$ is the frequency factor, $E_a$ the activation energy and $R$ the ideal gas constant.

Figure 29: Arrhenius plot for 5 reaction rate constants obtained with first-order fitting

Frequency factors ($k_0$) were calculated from the intercept ($\ln(k_0)$) and activation energies ($E_a$) from the slope ($-E_a/RT$). The values obtained for the five steps of the reaction are reported in the Table 11.
Table 11: Frequency factors and activation energies corresponding to the rate constants of the reaction

<table>
<thead>
<tr>
<th>Steps</th>
<th>$k_0$ (s$^{-1}$)</th>
<th>$E_a$ (kJ/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.5·10$^1$</td>
<td>8.13</td>
</tr>
<tr>
<td>2</td>
<td>9.2·10$^2$</td>
<td>15.8</td>
</tr>
<tr>
<td>3</td>
<td>5.8·10$^6$</td>
<td>28.9</td>
</tr>
<tr>
<td>4</td>
<td>9.8·10$^3$</td>
<td>82.1</td>
</tr>
<tr>
<td>5</td>
<td>3.6·10$^{15}$</td>
<td>19.9</td>
</tr>
</tbody>
</table>

As shown from the table, activation energies corresponding to $k_1$ and $k_2$ have relatively low values. The possibility of a physical limitation affecting both steps, such as mixing, is considered. Therefore, to investigate if activation energy of both steps is an intrinsic parameter, several experiments with higher flow rate of reactants were carried out.

Table 12: Conversion of PI as a function of temperature and reactants partial flow rate

<table>
<thead>
<tr>
<th>T (ºC)</th>
<th>Conversion ($Q_0=0.4$ ml/min)</th>
<th>Conversion ($Q_F=0.6$ ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.7</td>
<td>0.98</td>
</tr>
<tr>
<td>10</td>
<td>0.77</td>
<td>0.99</td>
</tr>
</tbody>
</table>

As shown in Table 12, results showed an increase of conversion of PI with an increase of flow rate. If the reaction was not limited by mixing, conversion should decrease (reaction time decreases when increasing flow rate), which is not the case. However, values of activation energy from steps 3, 4 and 5 corresponding to isomerisation, do not seem to be affected by such limitation. This is because the transformation of α- to β-ionone takes more time than cyclisation. In order to compare activation energy obtained with the one from batch studies, rate constant for α- to β-ionone transformation was calculated with equation 14 and plotted in Figure 30 in the form of Arrhenius plot. Equation 14 was obtained by combining equations 9 (int1 was not considered) and 10 and assuming steady state ($dC/int2/dt≈$0).

$$k_a = \frac{k_3·k_4}{k_4+k_5-k_4}$$  \hspace{1cm} \text{Eq. 14}
The activation energy for α-ionone transformation ($k_\alpha$) obtained from the fitting was quantified as ~74 kJ/mol which is comparable to the batch experiments (~65 kJ/mol). It indicates that the intrinsic kinetics of isomerisation has been achieved with the current MSR.

4.3.5. Conversion and yield

In all experiments, conversion of PI was comprised between 60% and 99%. The maximum yields for α- and β-ionones achieved were approximately 68% and 25% at 10°C and 3.32 s, respectively. The short reaction times in which the system operated does not allow higher β-ionone yield.

Conversion and yield were determined with equations 15 and 16, which consider no discrepancy in mass balance.

$$X_{PI} = \frac{C(PI)_{inlet} - C(PI)_{outlet}}{C(PI)_{inlet}} = \frac{C(\alpha) + C(\beta) + C(int 1) + C(int 2)}{C(PI)_{outlet} + C(\alpha) + C(\beta) + C(int 1) + C(int 2)} \quad \text{Eq. 15}$$

$$Y_\beta = \frac{C(\beta)}{C(PI)_{inlet}} = \frac{C(\beta)}{C(PI)_{outlet} + C(\alpha) + C(\beta) + C(int 1) + C(int 2)} \quad \text{Eq. 16}$$

The following graph shows the evolution of PI conversion with reaction time and temperature.
As expected, conversion decreases with decreasing temperature and reaction time. However, even at 0.84 s it is still high (~60%). This value gives an idea of the high rate at which PI disappears.

Finally, in order to verify mass balance, discrepancy was calculated for all experiments through equation 17.

\[
\% \Delta m = \frac{C(PI)_{inlet} - C(PI)_{outlet} - C(\alpha) - C(\beta) - C(int\,1) - C(int\,2)}{C(PI)_{inlet}} \cdot 100
\]

Eq. 17

% Δm >0: underbalance
% Δm <0: overbalance

The average discrepancy was found to be about 10%.
5. Conclusions and perspectives

5.1. Conclusions

In the present work cyclisation of PI has been studied. A microstructured cross-junction reactor with three inlets and one outlet was used to conduct experiments. Slug flow of reaction mixture was achieved through a two-phase fluid system consisting of NP and PFH.

In the first part, preliminary experiments regarding flow pattern and solubility of reaction species in PFH were carried out. After working with two types of MSR, PTFE and glass, the former was found to be the most suitable for the reaction to carry out. Flow rate for both reactants (PI and sulphuric acid) was fixed to 0.4 ml/min while PFH was set to 1 ml/min. Through other experiments, solubilities of NP, PI and ionones were quantified. Nitropropane mass transfer to PFH was found to be about 7.5%, while solubilities of PI and ionones to it were considered to be negligible.

In the second part, experiments with the aim of investigating intrinsic kinetics of cyclisation were performed. Analysis of reaction mixture through gas chromatography revealed the presence of a new species in the reaction. By following its concentration with reaction time, the behaviour of an intermediate was observed. A new kinetic mechanism has been therefore proposed, by taking into account state-of-the-art of the reaction and the additional intermediate detected. By fitting experimental data with the mechanism, kinetics has been found to be first order with respect to PI. However, the low values of activation energies calculated for cyclisation showed physical limitations in the system, probably due to mixing.

Thus, it can be concluded that a MSR can be used as a tool to investigate kinetics and reaction mechanism of fast and exothermic reactions, due to short residence times and isothermal conditions.

5.2. Perspectives

Considering experimental results obtained, several studies could be still done concerning the subject, the purpose of them being to investigate intrinsic kinetics of cyclisation.
In the future, the role of sulphuric acid in the reaction could be investigated. Given the high viscosity of the substance, when used in high concentrations, process is limited by mixing. Therefore, if it is feasible to work with a lower concentration of sulphuric acid, mixing time will be lower and intrinsic kinetics of cyclisation will be possibly reached.

Another future work could be oriented to mixing time in slug-flow which is never been quantified. This information would be useful for a priori prediction of operating conditions for different reaction conditions. The present investigations are relied on the assumption that the internal recirculations due to shearing action with capillary internal walls give good mixing.
6. References


20. W. Dobler, N. Bahr, K. Breuer, A. Kindler, B. Nicolaus, B. Klaus, D. Walter, and K. Alois. Continuous production of pseudoionone and ionone compounds, useful as perfume or intermediate for perfume, vitamin E or A or carotinoid, involves reacting aldehyde and excess ketone in aqueous alkali hydroxide solution. 2004
7. Appendix

7.1. Normalised concentration profiles

Figure 32: Normalised concentration of all species as a function of reaction time at $T=10^\circ C$

Figure 33: Normalised concentration of all species as a function of reaction time at $T=-10^\circ C$
7.2. Yield and selectivity

7.2.1. Yield and selectivity of α- and β-ionones as a function of reaction time

Figure 35: Selectivity (a) and yield (b) of α- and β-ionones as a function of reaction time at T=10°C
Figure 36: Selectivity (a) and yield (b) of α- and β-ionones as a function of reaction time at T=0°C

Figure 37: Selectivity (a) and yield (b) of α- and β-ionones as a function of reaction time at T=−10°C

Figure 38: Selectivity (a) and yield (b) of α- and β-ionones as a function of reaction time at T=−20°C
7.2.2. Yield and selectivity of α- and β-ionones as a function of temperature

*Figure 39:* Selectivity (a) and yield (b) of α- and β-ionones as a function of temperature at $\tau=0.84s$

*Figure 40:* Selectivity (a) and yield (b) of α- and β-ionones as a function of temperature at $\tau=1.68s$

*Figure 41:* Selectivity (a) and yield (b) of α- and β-ionones as a function of temperature at $\tau=3.32s$