Attempts towards the Catalytic Ketonization of Levulinic Acid to 2,5,8-nonanetrione

by

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ABSTRACT

ATTEMPTS TOWARDS THE CATALYTIC KETONIZATION OF LEVULINIC ACID TO 2,5,8-NONANETRIONE

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The ketonization of carboxylic acids to ketones has been explored since the mid 1800’s. However, the vast majority of studies focus on the use of carboxylic acids that do not possess any additional functional groups. Levulinic acid (LA), an important biomass derived platform chemical, presents both a carboxylic acid and a ketone functionality, which considerably increases the self-reactivity of this molecule. This is especially apparent at the high temperatures (300-400 °C) required for ketonizations over solid catalysts like CeO2/Al2O3 or ZrO2. The primary product of the ketonization of LA would be 2,5,8-nonanetrione (NTO) – which due to its structure – could be hydrogenated to the corresponding triol and applied as a 3D-crosslinker in the polymer industry. Prior attempts to produce this molecule required very complex synthetic routes and processes that could not be applied on industrial scale. Our goal was to develop a fixed-bed flow reactor that would promote the ketonization of LA in a one-step process; however, all attempts to obtain NTO in useful yields resulted in the formation of angelica lactones – the products of the self-reaction of LA – and 3-methyl-2-cyclopenten-1-one (3-MCP) which is the product of self-aldol condensation of the transient NTO, followed by further elimination of H2O and acetone. The mechanism and thermodynamic parameters of these reactions will be discussed in this thesis.
To my Grandmother (In Memoriam)
Acknowledgements

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<thead>
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<th>Abbreviation</th>
<th>Full Form</th>
</tr>
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<tbody>
<tr>
<td>2-MTHF</td>
<td>2-methyltetrahydrofuran</td>
</tr>
<tr>
<td>3-MCP</td>
<td>3-methyl-2-cyclopenten-1-one</td>
</tr>
<tr>
<td>α-AL</td>
<td>α-angelica lactone</td>
</tr>
<tr>
<td>β-AL</td>
<td>β-angelica lactone</td>
</tr>
<tr>
<td>DALA</td>
<td>Δ-aminolevulinic acid</td>
</tr>
<tr>
<td>DFT</td>
<td>Density Functional Theory</td>
</tr>
<tr>
<td>EG</td>
<td>Ethylene glycol</td>
</tr>
<tr>
<td>GVL</td>
<td>γ-valerolactone</td>
</tr>
<tr>
<td>HMF</td>
<td>5-hydroxymethyl furfural</td>
</tr>
<tr>
<td>LA</td>
<td>Levulinic acid</td>
</tr>
<tr>
<td>LACEA</td>
<td>3-(2-methyl-1,3-dioxolan-2-yl)propanoic acid also referred as levulinic acid cyclic ethylene acetal</td>
</tr>
<tr>
<td>LACEAHE</td>
<td>2-hydroxyethyl 3-(2-methyl-1,3-dioxolan-2-yl)propanoate also referred as levulinic acid cyclic ethylene acetal hydroxyethyl ester</td>
</tr>
<tr>
<td>LAEK</td>
<td>3-(2-methyl-1,3-dioxolan-2-yl)propanal also referred as levulinaldehyde ethylene ketal</td>
</tr>
<tr>
<td>LHSV</td>
<td>Liquid Hourly Space Velocity</td>
</tr>
<tr>
<td>RBF</td>
<td>Round-bottom flask</td>
</tr>
<tr>
<td>RM</td>
<td>Red mud</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>WHSV</td>
<td>Weight Hourly Space Velocity</td>
</tr>
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1. Introduction and Significance

Due to the growing demand for chemicals (e.g., polymers, solvents, fuels) and the concerns of society regarding CO₂ emissions and climate change, researchers are investigating the potential of biomass-based compounds to substitute fossil hydrocarbons as a source for either identical, or functionally equivalent chemicals.¹⁻¹² Considering the importance of biomass derived molecules, the US Department of Energy released a report identifying and exploring the production, properties and applications of the top 12 most prominent platform chemicals that could be sourced from biomass on a large scale.¹³ The platform chemicals explored in this thesis are obtained from a wide range of sources (e.g., starch, cellulose, hemicellulose, lignin, oil, protein).¹³ Depending on the reactions which they are subjected to, different chemicals can be produced, and they possess an extensive range of applications for industries such as textile, food supply, transportation, energy, communication, housing, recreation, health and hygiene.¹³

Levulinic Acid (4-oxopentanoic acid), LA, occupies a notable position on this list.¹¹,¹³⁻¹⁴ This results from its low production cost¹¹ and versatility.¹⁵ LA is one of the products that can be obtained from the treatment of 6-carbon sugars (sourced from starch or lignocellulosic biomass) with mineral acids (Scheme 1).¹⁶⁻²¹ LA can be used in the preparation of γ- Valerolactone (GVL),²² pentanoic acid,²³ α-Angelica lactone (α-AL) and β-Angelica lactone (β-AL), 2-Methyltetrahydrofuran (2-MTHF) and many other chemicals.¹³,¹⁵ Chart 1 summarizes some derivatives of LA.
Scheme 1. Reaction cascade leading from glucose (from cellulose) to LA.

Chart 1. Chemicals obtained through reactions with LA.\textsuperscript{13}

Ketonization of LA is one of the least explored reactions when considering this platform chemical. Ketonization, also referred to as ketonic decarboxylation, is the reaction of two equivalents of carboxylic acids producing a ketone and expelling CO\textsubscript{2} and H\textsubscript{2}O (Scheme 2). This reaction usually takes place at high temperatures in the presence of solid catalysts (e.g., CeO\textsubscript{2}, ZrO\textsubscript{2}, Al\textsubscript{2}O\textsubscript{3}, MnO\textsubscript{2} and others).\textsuperscript{9, 12, 24-43}

\[
R_1\text{COOH} + R_2\text{COOH} \rightarrow R_1\text{COR}_2 + \text{CO}_2 + \text{H}_2\text{O}
\]

Scheme 2. General reaction scheme for the ketonization reaction.
In addition, when considering the nature of the substrates subjected to ketonization, studies are concentrated in the application of substrates containing only the carboxylic acid functionality in the molecules.9, 12, 25, 28-29, 31-35, 42-44 This makes the ketonization of LA, a bifunctional molecule - that presents both a ketone and a carboxylic acid, an appealing and seemingly unexplored reaction. To date, only 2 articles present attempts towards the ketonization of LA, with one of them resulting in the production of the 2,5,8-nonanetrione (NTO) but also a variety of undesired side products. Schlaf and collaborators36 were responsible for one of these papers. They explored the use of red mud (RM) – a highly basic by-product of the Bayer Process used to extract Al₂O₃ from bauxite ores –36 to neutralize acidic bio-oils with LA being selected as the biomass derived acid to simulate the bio-oil. The reaction of this substrate with the highly complex RM, under reducing conditions, not only resulted in the production of the NTO through the ketonization of LA, but also 20 different compounds.36 The second paper exploring the ketonization of LA was published in 2018 during the course of this present study,45 and examined the same aspects covered in this project; however, the product composition was complex and inconclusive; this paper will be further discussed in Chapter 2.

Ketonic decarboxylation is usually performed in flow reactors.10, 24-25, 29, 32-34, 37, 46 The conditions applied in each of the experiments previously cited can vary considerably. Among the reaction parameters explored in the literature, feed flow rate, carrier gas composition (e.g., N₂, H₂, Ar) and flow rate, temperature, length/mass of catalyst bed and catalyst composition have received the most attention. Each of these reaction conditions can impact the production of the ketones in a specific way. Furthermore, the combination of different parameters also needs to be considered, because the response is usually dependent on the – possibly non-linear – interaction of reaction parameters.47-48
As previously mentioned, NTO is one of the main products of the ketonic decarboxylation of LA. Considering the structure of the molecule, its symmetry and distribution of carboxylic groups (Scheme 3), one could envision the hydrogenation of the ketone producing a triol. This molecule could then be used as a 3D-polymeric crosslinker, which would generate strong polymers in polyester or polyurethane formulations, or be further hydrogenated, producing alkanes with chain lengths in the range of gasoline and jet fuel.49

![Scheme 3](image)

**Scheme 3.** Hydrogenation of NTO to produce 2,5,8-nonanetriol and its 3D-representation.

Although this molecule possesses remarkable industrial application, its potential is still unexplored, especially due to the lack of large scale production processes. Only two strategies have been explored in the literature: (i) the first consists of a series of complex organic reactions with 4 to 7 steps depending on the starting reagents,50-53 which is a significant drawback when pursuing scale-up to industrial levels; (ii) the second method has a smaller number of steps,49,54-55 involving aldol condensation, hydrogenations and hydrolysis (Scheme 4).
Scheme 4. Production of nonane from HMF and acetone.\textsuperscript{49}

Although this method presents a smaller number of steps, achieving the ideal conditions is not trivial and different pathways leading to side products can be observed upon small variations in the reaction conditions. In addition, 5-hydroxymethyl furfural (HMF) is not an attractive starting material due to its extreme self-reactivity,\textsuperscript{56} which results in its fast deterioration. The combination of these difficulties compromises the application of this route on an industrial scale. This is one of the 7 times that the synthesis of NTO was reported in the literature,\textsuperscript{49-55} while the 2,5,8-nonanetriol synthesis was only reported once (Scheme 5).\textsuperscript{57}
Scheme 5. Synthetic route for the production of 2,5,8-nonanetriol.

The first impressions suggested that the application of LA to produce the NTO was a simple process to obtain this highly valuable chemical; however, this molecule also presents its drawbacks and challenges. Due to the presence of the ketone functionality, the decomposition of LA to the α-AL and β-AL is highly favorable at high temperatures over solid catalysts. This issue could be
mitigated by blocking the ketone functionality using protecting groups, such as ethylene glycol (EG), but this modification to the substrate introduces another level of complexity to the reaction, and the protecting groups may fall off at high temperatures and in the presence of acid and water.\textsuperscript{58-59} In addition to the self-reactivity of LA, Schlaf, \textit{et al.}\textsuperscript{36} demonstrated that the NTO can further react resulting in undesirable products, which are directly impacted by the reaction conditions under which the ketonization reactions are being performed.

Therefore, processes designed to produce high value chemicals by applying platform chemicals obtained from biomass are extremely important but can suffer due to self-reactivity of their substrates, directly resulting from the complexity of the starting materials. Bio-based platform chemicals open the possibility to not only replace fossil hydrocarbons and the products obtained through them, but also make feasible the production of molecules that cannot be achieved when applying crude oil. In this context, LA is a molecule that has the potential to substantially contribute to the production of chemicals from biomass. NTO is potentially extremely interesting and useful, though it has not received the proper attention, and can be extraordinarily difficult to obtain by other means. Hence, the desire of this project: to achieve a simple, single-step method applying LA as feed stock molecule to obtain NTO, using catalysts that are well-described in the literature.
2. Literature Review

2.1. Levulinic Acid

Levulinic acid is one of the most important platform chemicals obtained from biomass as featured in its high ranking presented by the US Department of Energy.\(^\text{13}\) LA can be obtained from two different sugar derived substrates, HMF and furfural, the first being obtained from the hydrolysis of raw cellulose through diluted acid treatment at high temperatures and the second using hemicellulose-derived pentoses.\(^\text{16-17, 60-62}\) The route starting from cellulose with HMF as an intermediate in the reaction (Scheme 6) has received more attention and is currently being applied at industrial scale.\(^\text{18-19, 60-61}\)

\[\text{Scheme 6. Proposed mechanism for the formation of LA from HMF.}^{20}\]

The first step in the mechanism of formation of LA (8) is the addition of water to HMF (1). This is a 2,3-addition of water catalyzed by acid and performed at high temperatures, resulting in 2. Following this is a dehydration of the alcohol portion of 2 generating the alkene 3. A second addition of water occurs, this time a 3,4-addition, producing 4. The next step involves the ring
opening of the hemiketal (4), followed by tautomerization and dehydration, which results in 6. The final step consists of a hydrolysis that eliminates formic acid and generates 7, which tautomerizes to LA (8).20

There are many different processes and catalysts being used to convert HMF into LA (e.g., the Biofine® process, homogeneous catalysts, heterogeneous solid catalysts, heterogeneous metal catalysts, solvolysis, ionic liquids and supercritical fluids), though most of these processes are still at the research level, and present drawbacks such as cost, production of undesired products, toxicity, and problems during the purification.61 To-date, the Biofine® process is the only one being employed at a commercial scale, as it give high yields at a remarkably low cost when compared with the other methods mentioned.18-19, 61

The Biofine® process is a patented method of LA production that applies acids (H$_2$SO$_4$) in low concentrations in very fast reactions. The process begins with cellulose sources such as paper mill waste, wood waste and agricultural residues.6 Different from other techniques, HMF is not the desired product, instead the Biofine® process directly leads to the 5-carbon products, LA and furfural.18-19 The production consists of an initial mixture of the feedstock material with diluted acid in a mixing tank. This mixture is then subjected to an acid hydrolysis, which produces HMF as an intermediate; this step is carried out in a plug-flow reactor, at 210-220 °C and 25 bar with a residence time of only 12 s. In the second stage, HMF is converted to LA in a larger reactor at 190-200 °C at 14 bar. Furfural and any other volatile products are removed at this stage. In the last stage, the insoluble mixture undergoes a dehydration, with LA being separated from solid decomposition products (humins), and the acid catalyst being recovered. The recycled acid catalyst is then fed back into the beginning of the process.18-19 As a result, LA is obtained in high yields.
and can be obtained in a purity of up to 98%. Figure 1 presents a simplified version of the steps applied in the Biofine® process.

![Diagram of the Biofine® process for conversion of cellulose to LA](image)

**Figure 1.** Biofine® process for conversion of cellulose to LA.\(^{19}\)

One of the plants in operation performing the production of LA from cellulose is located in Caserta, Italy and has a production capability of approximately 3000 tons/year (Figure 2).\(^{19}\) Estimations from the company responsible for the Biofine® process, predicted that if the process could be scaled to 1000-2000 dry tons/day, the price of LA would be considerably reduced to around $0.09-0.11/kg, which would make the application of LA as large scale feedstock in biorefineries a possibly attractive business opportunity.\(^{19, 21}\)
LA has attracted the attention of many industries – especially when considering its versatility and production price – and has a number of different applications such as “textile dye, antifreeze, animal feed, ink and coating material, solvent, food flavoring agent, component of pharmaceutical compounds, resin, synthetic rubbers, material for batteries and even cosmetics.” In addition, the derivatives of LA also have a range of applications including fuel extenders (e.g. 2-methyltetrahydrofuran (2-MTHF)), biodegradable herbicides (e.g. Δ-aminolevulinic acid (DALA)), monomers (e.g. diphenolic acid (4,4-bis(p-hydroxyphenyl)pentanoic acid)) and solvents (e.g. tetrahydrofuran (THF) and GVL). In addition to the applications mentioned, DuPont® has also patented a wide range of LA derivatives which are applied in a range of products.

Although LA presents a wide range of derivatives (Chart 1), only two groups, including the Schlaf group, have attempted to perform direct ketonic decarboxylation of this platform chemical. The attempts performed by the Schlaf group, resulted in the formation of a mixture of
approximately 20 different products due to the complexity of the RM catalyst applied and other reaction conditions;\textsuperscript{36} these results diminished the potential of this specific set of parameters to perform an industrially applicable ketonization of LA. The second attempt using LA as a starting material in a direct ketonization produced unsatisfactory results and the data presented was inconclusive.\textsuperscript{45} On the other hand, other attempts were explored in order to achieve carbon chains with 9 carbons starting from LA.\textsuperscript{11} In one of these processes, LA was reduced to GVL that was then converted to pentanoic acid which was subjected to ketonization, producing 5-nonanone; this ketone was subsequently hydrodeoxygenated to nonane.\textsuperscript{11}

2.2. Ketonization

As previously mentioned, ketonic decarboxylation, or ketonization, is a reaction where 2 equivalents of carboxylic acids are combined and undergo decarboxylation and dehydration, yielding one equivalent of a ketone, carbon dioxide and water. This process is widely applied to produce symmetric ketones and the first application dates back to 1858.\textsuperscript{64} The process used at that time was slightly different from the current methods and applied a dry distillation of calcium acetate to yield acetone.\textsuperscript{9, 31} Most current methods apply heterogeneous catalysts to convert two equivalents of carboxylic acids into their symmetric ketone, while also producing CO\textsubscript{2} and H\textsubscript{2}O as side products (Scheme 2).\textsuperscript{9, 12, 25-36, 38, 40-43, 65} These reactions occur at elevated temperatures, resulting in the interaction of the molecules of acid in the gaseous state with the solid surface of the catalyst, promoting the ketone formation.

Studies of the ketonic decarboxylation resulted in the development of different mechanistic models to explain the experimental observations and a wide range of heterogeneous catalysts being studied under a variety of conditions. Considering the mechanisms, there is still some disagreement among
researchers, but the β-keto acid pathway is one of the most accepted ones. In this mechanism, ketonization occurs mainly at the surface of the catalyst and involves the formation – as the name suggests – of a β-keto acid intermediate.\textsuperscript{9-10, 66-68} This mechanism was studied using Density Functional Theory (DFT) calculations for the reaction of acetic acid on a \emph{m}-ZrO\textsubscript{2} surface,\textsuperscript{10} and was used to explain results with other catalysts and substrates, including cross ketonizations.\textsuperscript{66-68} Regarding catalyst development, there are also many studies exploring different transition metals, alkali and alkaline earth oxides and catalyst supports. The vast majority of these studies employ CeO\textsubscript{2}, ZrO\textsubscript{2} and MnO\textsubscript{2} as the most active catalysts to perform surface catalyzed ketonization, especially when these oxides are supported in Al\textsubscript{2}O\textsubscript{3}, TiO\textsubscript{2} and SiO\textsubscript{2}.\textsuperscript{9, 25, 29-30, 40} In addition, reaction conditions were varied depending on the catalysts and substrates used. Among these parameters, temperature, feed flow and carrier gas (composition and flow) have received the most attention. Therefore, all the factors mentioned above must be taken into consideration when designing an experiment to achieve consistent results.

\textbf{2.2.1. Mechanism}

As already stated, the β-keto acid route received significant support from the scientific community, especially after the DFT studies were carried out.\textsuperscript{9-10} This mechanism receives its name due to the formation of the β-keto acid intermediate. Scheme 7 presents a simplified view of the steps involved in this mechanism on the surface of \emph{m}-ZrO\textsubscript{2} (where “m” designates monoclinic).
Scheme 7. Reaction mechanism involving the β-keto acid intermediate.\textsuperscript{10}

As Scheme 7 shows, the first step involves the dissociative adsorption of two molecules of acetic acid on the surface of the catalyst; in this case the bond formation occurs between the oxygens of the acid and the metal centers of the catalyst. The second step involves the abstraction of an α-hydrogen. This step is important as, many studies provided evidence that without the presence of these hydrogens, the ketonization cannot occur.\textsuperscript{9-10, 27, 31, 42} Also during the previous step, one of the hydroxyl groups (-OH) is abstracted from one of the acids; the combination of this hydroxyl group with the α-hydrogen will later promote the formation of the H\textsubscript{2}O molecule. The next step, for which the reaction is named, consists of the nucleophilic attack of the double bond of the deprotonated acid enolate (red) to the carbon deficient in electron density of the second acid (black), forming the β-keto acid intermediate. Concomitantly to this attack, the decarboxylation occurs, and CO\textsubscript{2} is released. Subsequently, the ketone and H\textsubscript{2}O are also released. According to DFT calculations, although many endergonic steps are present, the overall reaction is exergonic and the formation of the ketone is kinetically and thermodynamically favorable through the β-keto acid route (Figure 3).\textsuperscript{10, 67}
Figure 3. Energy profile calculated by DFT-D3 for the ketonic decarboxylation of acetic acid over m-ZrO$_2$.$^{67}$

2.2.2. Heterogeneous catalysts

As previously discussed, heterogeneous catalysts, especially oxides, are widely applied in ketonic decarboxylation. Comprehensive reviews such as the one written by Pham, et al.$^9$ and other articles exploring catalyst preparation$^{27, 41, 65, 69-70}$ highlight the most relevant features that promote the occurrence or not of ketonization. Among the aspects discussed, the lattice-energy of the oxides, their basicity or acidity and the use of supports received special attention.$^{9, 27, 41, 65, 69}$

The lattice energy it is one of the parameters that define if the reaction will occur with the formation of a bulk carboxylate or if surface reactions are more likely to occur. The lattice energy defines the strength of the bonds between the metals (M) and the oxygens (O) in the catalyst. Low-lattice energies usually facilitate the formation of bulk carboxylates, due to the weak M-O interaction; this is usually observed on basic oxides or alkali and alkaline earth oxides.$^{9, 27}$ Alternatively, metal oxides such as CeO$_2$ and ZrO$_2$ have higher lattice-energies and, in these cases, the surface reactions are more likely to happen, as the break-up of the M-O bond network required for the formation of
carboxylates is thermodynamically less favorable.\textsuperscript{9} Considering the problems associated with the formation of bulk carboxylates (e.g., deactivation of catalytic sites, change in the structure of the oxides among others), catalysts able to perform surface reactions are more desirable.\textsuperscript{41, 65, 69}

The nature of the surface sites available for ketonization is the second aspect that receives considerable attention. Research has shown that amphoteric sites on the catalyst surface are especially desirable.\textsuperscript{9, 12, 27, 65, 69} This results from the fact that catalysts such as MgO, which are highly basic, are more likely to promote the formation of bulk carboxylates. Alternatively, oxides with amphoteric characteristics can interact with the different species present or the ones formed during the ketonization (Scheme 7). The basic sites are responsible for deprotonating the carboxylic acids, while the acidic sites coordinate with the acid (substrate) and stabilize the β-keto acid intermediate, i.e., cooperative effects are likely important. In order to promote these interactions, the cations and oxygen anions at the surface need to be coordinatively unsaturated.\textsuperscript{9}

Due to their amphoteric properties, CeO\textsubscript{2}, ZrO\textsubscript{2} and MnO\textsubscript{2} are the most recommended catalysts for ketonic decarboxylation.\textsuperscript{9, 65, 69}

In addition to the modifications directly performed in the oxides, the use of supports is also widely explored and desirable. Supports are applied to provide a higher number of effective interactions between the substrate and the catalyst sites, which is especially important when using supports with high surface area. In addition, research has shown that pure oxides such as CeO\textsubscript{2}, suffer considerable deactivation when used as a pure oxide, observed through the formation of CeO\textsubscript{2} whiskers after reaction with carboxylic acids.\textsuperscript{41, 65, 69} Having the active phase dispersed in a support improves the substrate-catalyst interaction and increases the exposure of the active sites of the catalyst, while at the same time requiring a lower amount of the most expensive catalytically active metal (oxide). Among the supports explored (e.g., Al\textsubscript{2}O\textsubscript{3}, SiO\textsubscript{2}, TiO\textsubscript{2}) the best results were
obtained when using Al₂O₃, especially because this oxide was also able to perform ketonization by itself.⁹, ²⁵, ²⁹, ⁴⁰ Therefore, catalytic systems based on CeO₂/Al₂O₃ and ZrO₂ combine all the properties previously highlighted, making them remarkable catalysts for ketonic decarboxylation.

2.2.3. Reaction conditions

Defining the reaction conditions under which the ketonization will be performed is a crucial step. Temperature, carrier gas composition, gas flow and feed flow, are among the parameters that can be adjusted to achieve optimal results.

Temperature is a parameter that deserves discussion and can considerably change how the reaction takes place and how the catalyst responds to the interaction with the substrate. In general, most of the studies are performed with the reaction temperature varying from 300 to 450 ºC,²⁵-²⁸, ³², ³⁴ with this temperature range ensuring that the substrate is in the gas phase and the substrate-catalyst interaction happens at the gas-solid interface. However, studies were also performed at lower temperatures, i.e., as condensed phase catalytic reactions.⁴¹

As mentioned, the temperature of the reaction will change how the catalyst responds to the contact with the substrate, and the major difference is the formation of bulk acetates instead of having surface catalyzed, i.e., superficial reactions.⁹ Studies performed by Snell and Shanks⁶⁵ with CeO₂ and by Kuriacose and Jewur⁷¹ with iron oxide demonstrated that in the temperature range of 150 to 300 ºC the catalyst structure is modified after reacting with the substrate due to the formation of bulk carboxylates. However, when the ketonization is performed between 300 and 400 ºC the formation of bulk carboxylates is consistently reduced, and the superficial reaction is the route by which the ketonization takes place. Therefore, the temperature range of 300 to 400 ºC is the most reliable to achieve high conversion and reduce catalyst deactivation or morphological changes.
The carrier gas composition is another aspect that can also affect the reaction and by extension, the products obtained, especially when considering LA. Studies about different carrier gases are limited, with Zaytseva, et al. recently publishing a study comparing the impact of N₂ (non-reactive gas) and H₂ (reducing agent) in the ketonization of pentanoic acid using CeO₂/ZrO₂ catalysts. The results showed that the composition of the carrier gas did not considerably impact the products and conversions obtained. In fact, most of the published studies use either H₂ or N₂ in their ketonization reactions without major impacts of the products obtained; however, those studies were performed with substrates that do not present other organic functions besides the carboxylic acid. When considering LA, the carrier gas can considerably impact the products obtained. Reactions performed with H₂ can result in the formation of products such as GVL, which can be further hydrogenated to pentanoic acid that can undergo ketonization to yield 5-nonanone (Scheme 8). As a result, avoiding the use of H₂ as a carrier gas in ketonization reactions with LA is desirable to mainly yield the production of NTO and avoid the formation of hydrogenation products.
Scheme 8. Side reactions of LA in the presence of H_2.

Gas flow and feed flow are factors that can be considered related to each other. These two parameters are useful to define the gas phase residence time in the catalytic zone and the Weight Hourly Space Velocity (WHSV).\textsuperscript{72} The equations below present the calculations applied to determine these values (when calculating WHSV for pure compounds, the substrate concentration is replaced by the density of the liquid).

\[
WHSV = \frac{\text{mass flow rate (g.h}^{-1})}{\text{catalyst mass (g)}} = \frac{\text{substrate conc (g mL)}^{-1} \times \text{liquid feed rate (mL min}^{-1}) \times 60 \text{ min}}{\text{catalyst mass (g)}} \quad \text{Eq. 1}
\]

\[
\text{Residence time (s)} = \frac{\text{volume catalytic zone (cm}^3)}{\text{carrier gas flow rate (cm}^3 \text{ min}^{-1}) \times \frac{1 \text{ min}}{60 \text{ s}}} \quad \text{Eq. 2}
\]

Residence time is a crucial aspect in ketonization reactions of LA. When precisely adjusted, this parameter could avoid the occurrence of side reactions and coke formation, resulting from the production of ALs (Scheme 9).\textsuperscript{36} Coke results from the uncontrollable decomposition of substrate and products in the surface of solid catalysts, its presence, blocks the active sites in the catalyst
surface, reducing its capacity to positively interact with the substrate and to participate in the reactions.

The study performed by Taimoor, et al.\textsuperscript{37} using acetic acid in the presence of $\gamma$-Fe$_2$O$_3$ (maghemite) showed that low feed flows improved the yield of acetone obtained. In the study carried out by Glinski, et al.\textsuperscript{25} reactions performed between 300 and 350 °C are highly affected by the increase in Liquid Hourly Space Velocity (LHSV). Increasing the LHSV considerably decreased the conversion of acetic acid to acetone. However, in reactions performed above 350 °C, the LHSV did not play an essential role in the conversion of acetic acid. Batch reactions, which necessarily result in very long contact times between the substrate or products and catalyst, performed by the Schlaf group and collaborators using LA and red mud as a catalyst,\textsuperscript{36} resulted in the formation of up to 20 different products and a considerable change in the catalyst structure as well as substantial coke formation.

\begin{equation}
\text{O} \quad \text{OH} \quad \text{O} \quad \text{CO} \quad \text{c} \quad \text{oke}
\end{equation}

\textbf{Scheme 9.} Coke formation from angelica-lactone.\textsuperscript{36}

Schemes 8 and 9 give a general idea of possible byproducts that can be obtained from LA in ketonization conditions before producing the desired ketone (NTO). One aspect is common for most of the reactions presented, the formation of H$_2$O. As a result, this is another parameter that can be altered to maximize the main:side product ratio. Although, the ketonization of LA also generates water as one the products, having the LA combined with H$_2$O in the feed stream may considerably reduce the formation of side products, which result from dehydration and
condensation (e.g., aldol) reactions, and avoid the irreversible formation of coke, as it should impact the undesirable formation of angelica lactones. This introduces another parameter for the experiments, considering that the content of water can be varied. The thermodynamics of the reactions previously mentioned and other reactions will be explored further in this thesis.

As can be observed, not only altering one of the experimental parameters affects the results obtained in ketonization reactions, but also the association of these parameters can considerably impact the products obtained.

2.3. 2,5,8-nonanetrione

As stated, the main goal in performing the ketonic decarboxylation of LA is the production of the triketone, 2,5,8-nonanetrione. This molecule had its first synthesis performed by Alder and Schmidt \(^{50}\) in 1943, starting from [5-methyl-furfuryl]-acetone. The next attempt was performed in 1976, in a synthesis starting with butanone and paraformaldehyde in ethanol, with several steps and 7 different reagents.\(^ {51}\) Approximately 10 years later, in 1987,\(^ {52}\) a new synthetic route was developed starting from 1,5-dicarbonyl compounds, although the number of steps and reagents involved was also considerably large. In 1993,\(^ {53}\) the third synthetic route involved the preparation of levulinic aldehyde that was refluxed with 4 different reagents in ethanol, and 4 extra steps were necessary to achieve the final product. More recently NTO was produced starting from the product of an aldol condensation between HMF and acetone (Scheme 10).\(^ {49,54-55}\)
Scheme 10. Steps involved in the production of NTO starting from HMF.\textsuperscript{49}

The reaction is comprised of (i) an aldol condensation of HMF and acetone; (ii) hydrogenolysis of the alcohol; (iii) hydrogenation of the double bond formed in the condensation; and (iv) subsequent hydrolysis of the product, resulting in the formation of NTO.\textsuperscript{49} This synthetic route can be compromised by small variations on reaction conditions; in addition, having HMF as a starting material is not ideal, due the high reactivity of this molecule that is simultaneously a furan, a benzylic aldehyde/alcohol and a cyclic bis-enol.\textsuperscript{56}

The synthesis of 2,5,8-nanonatriol (the hydrogenation product of NTO) also suffers the same problems encountered for NTO. A synthetic route was attempted in 2013 (Scheme 5),\textsuperscript{57} being the only reported route thus far. This organic synthesis is as complicated as the organic routes applied in the synthesis of NTO. It involves a total of 7 steps and very complex reagents and solvents, has a low yield, an undesirable atom efficiency and e-Factor, noxious waste generation, and this is not applicable on a large scale.

The lack of synthetic routes that could be transferred to industrial scale stimulated the application of ketonic decarboxylation of LA to produce NTO. The first attempt was performed by the Schlaf group and collaborators seeking to use RM – bauxite mining waste – as a sacrificial catalyst to neutralize bio-oil, which contains LA.\textsuperscript{36} One example of a GC-EI-MS trace from the product
mixture obtained after a reaction using LA and RM performed at 200 ºC in a batch reactor under H₂ pressure (800 psi) can be seen in Figure 4.

![Figure 4](image)

**Figure 4.** GC-EI-MS trace for the liquid products obtained in the reaction between LA and RM at 200 ºC under 800 psi of H₂.³⁶

As can be observed, due to the complexity of the catalyst, which is composed of α-Fe₂O₃, α-FeO(OH), Al₂O₃, SiO₂, TiO₂, CaO, Na₂O and other residues (Figure 5),³⁶, ⁷³-⁷⁶ and the reaction conditions applied (batch reactor under H₂ atmosphere), the reaction resulted in the production of NTO and 19 other products,³⁶ precluding the use of RM as a ketonic decarboxylation catalyst. Nevertheless, the presence of NTO as one of the products during these reactions sparked the idea of using catalysts specially designed to perform ketonizations.
Prior to the beginning of this project, the application of ketonization catalysts on flow reactions with LA had never being attempted; however, after our first year of experiments, we came across a paper prepared by a research group in the United States, which was accepted for publication in June of 2017. Lilga et al. were exploring very similar reaction parameters to the ones being studied in this project. Among the reactions performed, they employed aqueous solutions of LA and EG, some reducing agent solutions using formic acid, and aqueous solutions of LA and GVL; in addition, they also prepared the LA ketal using EG and performed reactions using a solution of the ketal with H₂O. Even though some of the reactions attempted had similarities with the ones explored on this project, they were not able to perform clear characterization of their reaction products, as can be observed in Figure 6. Furthermore, some experimental parameters applied resulted on unexpected products, the most evident being the reaction applying LA ketal in H₂O.
Ketals can be hydrolyzed in acidic conditions and considering that only the ketone portion of LA is protected with the EG, the carboxylic acid was strong enough to promote the deprotection of the substrate.\textsuperscript{58}

\textbf{Figure 6.} Data extracted from Ref 45 representing results of ketonization reactions.

The general impression from the GC-EI-MS traces ((a) products for the reaction of a aqueous solution of LA/EG 1:1 mol ratio at 330 \textdegree C, (b) products for the reaction of a aqueous solution of LA/EG 1:1 mol ratio at 380 \textdegree C, (c) products for the reaction of a aqueous solution of GVL/EG 1:1 mol at 380 \textdegree C, (d) products for the reaction of a aqueous solution of GVL 6.5 wt\% at 380 \textdegree C) provided in Figure 6 is that there is no clear separation among the different products obtained in
the different reactions performed by Lilga, *et al.* and there is no clear confirmation that the ketonization actually happened, considering that none of the peaks are assigned to NTO or any of the products that could be obtained from it. As a result, these results can be considered inconclusive, especially when considering the complex product composition. Therefore, there is still a void in the literature regarding the ketonization of LA, and one of the main goals of this project is to fill this void with reliable data analysis of a wide range of reactions that explore many experimental parameters that affect the ketonization of LA.

There is a large range of possible reactions that can occur with LA and further reactions of the products in ketonization conditions. Scheme 11 presents the hypothetical products obtained using LA while performing ketonization in an inert atmosphere and the reactions that can occur with the products in these conditions. The reactions involve products obtained through ketonization, decarboxylation or dehydration of LA and its products.

![Scheme 11. Hypothetical reaction cascade in the ketonization of LA.](image)

Many other products can be envisioned in the conditions applied during a ketonization reaction, so defining a pathway for the formation of the most favorable products under catalytic conditions.
is extremely complex. This is affected by the nature of molecules and catalysts involved, the interactions between them, the different conditions that need to be optimized and the possible intermediates. However, computational chemistry methods can be used to generate a thermochemical map that, even lacking the calculation of activation barriers and surface effects, can be used to determine which products and reactions are thermodynamically feasible. A thermochemical map was generated for this project analyzing the ketonization of LA performed at 400 ºC, with the results being presented and discussed in the following sections.

2.4. Overcoming the self-reactivity of levulinic acid

As previously pointed out, due to the presence of both a ketone and a carboxylic acid functionality in the LA molecule, there is great potential for the self-reactivity of LA molecules. In addition, this self-reactivity is not only restricted to the substrate, the products obtained through the ketonization reaction can also self-react, generating undesirable side products and humins\(^77\) – which are undefined compounds that result from uncontrollable polymerization of substrate with itself or with products. They can be both liquid and solid and generally have a dark color. Although the goal of this project is to keep the ketonization reactions as simple as possible, overcoming the self-reactivity of LA without performing any alterations to the substrate is challenging. As a result, ketonization reactions were also performed applying protected ketal versions of LA.

The protection of LA and similar molecules is well-explored in literature.\(^59, 78-80\) In this project the synthetic route applied by Moreau, \textit{et al.} was the one selected to be performed.\(^79\) In this reaction, LA reacts with excess EG in benzene under Dean-Stark conditions, and following the remaining reaction steps, levulinic acid cyclic ethylene acetal (LACEA) is obtained as the final product. The
experimental parameters and the results for the reactions with this substrate will be explored in the following sections. Scheme 12 illustrates the reaction to prepare the ketal.

Scheme 12. Reaction scheme for the preparation of LACEA following the procedure in Ref 79.

As can be observed, the product of this reaction is a molecule with a ketal group in the place where the ketone on LA was and this, in principle, should reduce the self-reactivity of LA avoiding intramolecular reactions. However, two factors need to be taken into consideration. As previously mentioned, hydrolysis of the ketal can occur in the presence of acid, this requires that any reagent used in the ketonization reaction be completely dry, but even this might not completely avoid the deprotection. Considering that water is one of the products of the ketonization, the humid environment generated by the ketonization can contribute to the hydrolysis of the ketal inside of the reactor. If the presence of water could not be avoided, a secondary alternative would be the utilization of the levulinic acid cyclic ethylene acetal hydroxyethyl ester (LACEAHE), the first intermediate in Scheme 12. This intermediate can be isolated and applied as a substrate in ketonization reactions but, the advantage of this substrate is also its drawback, as the ester does not possess a carboxylic acid functionality. This would avoid the deprotection of the ketal; however, because ketonization reactions occur between carboxylic acids, the presence of an ester instead of a carboxylic acid might completely stop any reaction from happening. The thermal stability of the LA ketal is another drawback. Some of the LA ketals reported in literature are only stable up to 300 °C, with greater temperatures promoting the deprotection of the ketals. This is an issue because ketonizations take place above 300 °C and, as a result, the high temperatures in
which they are performed might promote the deprotection of the ketal before the desired reaction takes place.

Even though the use of LA ketals does not guarantee that side intramolecular reactions will not occur, the application of this protected substrate can be considered a reasonable alternative to overcome the self-reactivity of LA.
3. Overview of the Project

To date, the synthesis of NTO has only been marginally explored. In addition, most of the attempts to obtain NTO relied on complex organic synthetic routes\textsuperscript{49-55} that present a large number of steps or a combination of reagents and solvents that cannot be explored in large scale, diminishing the industrial potential of NTO.

The alternative production of NTO by performing a ketonic decarboxylation of LA\textsuperscript{36} was attempted using a promiscuous catalyst composed of a large number of oxides that promote the formation of approximately 20 different products. As a result, this project aimed to close this gap and efficiently apply a catalyst system able to promote the ketonization of LA to yield NTO.

A flow reactor with a fixed catalyst bed was designed and built to perform the ketonic decarboxylation of LA (Scheme 15 and Figure 29). At least 4 different experimental parameters (section 6) were altered in the reaction and the interactions of these parameters were explored. In addition, reactions applying ketal versions of LA, which were characterized using \textsuperscript{1}H and \textsuperscript{13}C NMR and GC-EI-MS, were also explored to reduce the self-reactivity of the substrate. The products of the reactions were analyzed using GC-EI-MS and the data is provided and discussed in sections 4, 5 and in the Appendix C.

The supported heterogeneous catalyst, CeO\textsubscript{2}/Al\textsubscript{2}O\textsubscript{3}, was prepared for the ketonization of LA (section 6) and characterized before and after the reactions using XRD (sections 4 and 5).
4. Results

This section highlights the main findings obtained applying a batch reactor and the fixed-bed flow reactor designed and built to perform the ketonic decarboxylation of LA and LA ketals.

4.1. Thermochemical map for the ketonization of levulinic acid

A thermochemical map represents an “energy landscape” of possible reaction pathways and gives information about the relative thermodynamic feasibility of the pathways. Here we present a thermochemical map for the reactions of Scheme 11. Employing the Gaussian 09 software package, the method applied in the calculations performed was DFT-B3LYP; the basis set used in the optimization was 6-311G ++(2d p) and all the calculations were performed at a temperature of 400 °C (673 K), i.e., in the gas phase. Figure 7 presents the thermochemical map obtained. Note that this thermochemical map makes no statement about the mechanism and kinetics of the reactions and therefore also does not consider activation barriers and the effect of any catalysts present.
Aiming to create a meaningful comparison between the different products, the energies for all reaction products were calculated relative to the energy of LA (energy set to 0 kcal/mol). Hess’s law was applied, and the values displayed in Figure 7 are the values of energy for the reactions generating the specific molecules in each case; as a result, the energy of any individual molecule is meaningless (the actual energies obtained from the DFT calculations and used are listed in Appendix E). Thermodynamically NTO and butanone are the most favorable products obtained directly from LA, with relative ΔG values that are considerably more negative than those for the formation of α-AL. Both the reaction to 2-butanone and NTO generate CO₂, which makes them entropically very favorable. Although the formation of butanone is thermodynamically more favorable than NTO, and as previously expressed, there is a possibility of intramolecular reactions with NTO and eventual formation of 3-MCP and acetone, the thermodynamic sink for this route.

**Figure 7.** Thermochemical map for the products in the ketonization reaction of LA.
4.2. Catalyst characterization: X-ray powder diffraction (XRD)

The CeO$_2$/Al$_2$O$_3$ catalyst was prepared by impregnation of a Ce(NO$_3$)$_3$ solution into activated Al$_2$O$_3$ as described in detail in the Experimental Section and in the literature.$^{25}$ In order to confirm the deposition of CeO$_2$ on the surface of the Al$_2$O$_3$ pellets, XRD data was acquired for the catalyst (CeO$_2$/Al$_2$O$_3$ 20wt%) and the support (Al$_2$O$_3$). The data is presented in Figure 8.

![Figure 8. Powder XRD patterns of Al$_2$O$_3$ and CeO$_2$/Al$_2$O$_3$ 20wt%.](image)

The pattern for the Al$_2$O$_3$ could not be fitted to one single known pattern. In fact, this sample has patterns that fit multiple phases of Al$_2$O$_3$. The pattern for the catalyst, CeO$_2$/Al$_2$O$_3$ 20wt%, presents some peaks that are also observed for the support; however, the disappearance of some peaks and appearance of others confirm the formation of CeO$_2$ on the Al$_2$O$_3$ surface (PDF number 2-1306). When the samples were being prepared for the XRD analysis, it was possible to observe that the impregnation was satisfactory and not only the surface of the Al$_2$O$_3$ pellets had CeO$_2$ (pale-yellow
color), but also the bulk region of the support, which confirms that the Al$_2$O$_3$ pores were also impregnated.

The CeO$_2$/Al$_2$O$_3$ catalyst was also submitted to XRD analysis after its use in the ketonization reactions. The comparison between the catalyst before and after a ketonization reaction can be seen in Figure 9.

![Figure 9](image.png)

**Figure 9.** Powder XRD patterns of CeO$_2$/Al$_2$O$_3$ 20wt% before and after ketonization reactions.

As Figure 9 shows, the difference between the XRD patterns for the two samples is minimal, only generating variations in the intensity of the peaks. The sample after the ketonization reaction had a black color indicating some coke deposition. When preparing the sample for the XRD analysis, it was possible to observe that the substrate and possibly products also reacted inside the pores of the catalyst, which was confirmed because the crushed pellets were completely black in the inside as well as on the outside surface.
4.3. Ketonizations in batch reactor

Considering the formation of NTO in batch conditions previously performed by the Schlaf group applying RM, the first tests to produce NTO using the ketonization catalyst CeO$_2$/Al$_2$O$_3$ 20wt% were also performed under batch conditions. In addition to the reactions performed with the prepared catalyst, commercially obtained ZrO$_2$ and RM were also explored for ketonizations in batch conditions.

The temperature and pressure were monitored during the entire process, providing information about the progress of the reaction. Figure 10 presents the temperature and pressure evolution for the reaction performed at 400 °C using only LA and the catalyst CeO$_2$/Al$_2$O$_3$ 20wt%.

![Figure 10. Pressure and temperature evolution for the ketonization of LA at 400 °C with CeO$_2$/Al$_2$O$_3$ 20wt%.

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The only event observed in the temperature evolution before reaching 400 °C was around 240 °C, with the decrease in temperature being due to the vaporization of LA (B.P. of 245 °C). Prior to this, the variation in pressure was almost imperceptible. The reactions at other temperatures and substrate conditions (mixture 1:1 of LA:H$_2$O) were also monitored (Appendix D, Figures D3 and D5). The same behavior was observed for the other conditions, with the differences being the total time of reaction, the final pressure and temperature achieved.

The contact time of the catalyst with the substrates and products formed varied from 100 to 200 min depending on the final temperature. The final product observed at the end of the reactions was a viscous black liquid and solid coke, especially covering the catalyst, though some of the reactions also produced a clear liquid. Depending on the conditions, the color of the liquid slightly changed, being transparent with black organic drops dispersed in it, or orange, especially when using H$_2$O in the reaction. This liquid is mainly aqueous with many products in it; GC-EI-MS analyses were performed and will be presented later. Figure 11 shows a representative image of the bottom of the reactor after the reaction and the liquid produced for the reaction of LA with CeO$_2$/Al$_2$O$_3$ 20wt% at 400 °C.
As previously mentioned, the liquid obtained from the reaction of LA with CeO$_2$/Al$_2$O$_3$ was submitted to GC-EI-MS analysis. Figure 12 presents a comparison among the GC-EI-MS traces for the reactions performed with this catalyst at temperatures varying from 300 to 400 °C. The liquid samples present a complex mixture of different compounds including $\alpha$-AL (match of m/z and fragmentation pattern using reference samples), butanone and 3-MCP (both matches of m/z and fragmentation pattern against NIST 98 library search), acetone, which also confirms the formation of 3-MCP and unidentified products. However, no traces of NTO were observed.
Figure 12. GC-EI-MS traces of liquid products for ketonizations of LA with temperatures varying from 300 to 400 °C with the catalyst CeO$_2$/Al$_2$O$_3$ 20wt%.
Water is a by-product in both, the desired ketonization reaction and of the side-reactions starting from LA (Scheme 11). As a result, a reasonable strategy to reduce the occurrence of these reactions would be to suppress those reactions applying an aqueous solution of LA. Part of the results (GC-EI-MS traces) obtained for the products of reactions starting with 1:1 wt% aqueous solutions of LA/H₂O at temperatures varying from 300 to 400 °C utilizing CeO₂/Al₂O₃ 20wt% can be seen on Figure 13.

**Figure 13.** GC-EI-MS traces of liquid products for ketonizations of aqueous solutions of LA:H₂O 1:1 wt% with temperatures varying from 300 to 400 °C with CeO₂/Al₂O₃ 20wt%.
Note that the aqueous solutions, which were used to obtain the GC-EI-MS data do not always contain a complete composition of the possible products obtained at end of the reactions, because no meaningful analysis could be performed to the black oils generated.

Reactions were also performed applying the same conditions as the ones attempted by Schlaf et al with RM.\textsuperscript{36} In this case, no H$_2$ was added to the system, and the results can be seen in Figure 14.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure14.png}
\caption{GC-EI-MS traces of liquid products for ketonizations of LA with RM at 200 °C.}
\end{figure}
The results were very similar to the ones obtained by the Schlaf group in their attempts (NTO was not observed in the reactions performed on this project) and the ones being previously observed in other batch reactions performed with different catalysts. This, however, was the first time that another one of the products obtained from further reaction of NTO was observed. This product is a result of an internal aldol condensation of NTO with subsequent elimination of H₂O (Scheme 11).

The unsatisfactory results (in terms of NTO production) obtained in batch conditions stimulated the development and application of alternative methods such as reactions in a RBF system and the use of a fixed-bed flow reactor designed to perform the ketonization of LA. By doing this, the contact time between LA and its reaction products with the catalyst can be adjusted and considerably reduced; as a result, the formation of stable NTO was hypothesized to be more probable.

4.4. Ketonization in a RBF system

The contact time between LA and its reaction products with the catalyst was an issue identified when analyzing the data obtained for the reactions in the batch reactor. The long contact time was mainly attributed to the fact that the reactor needed to reach the desired temperature and was kept at that temperature for at least 1 h. One strategy to reduce the contact time of substrate and catalyst was to use a round bottom flask (RBF) instead of a sealed reactor. An image of the reaction setup is given in the Experimental section (Figure 28) This change reduced the heating times varying from 10 to 35 min to reach 350 ºC, depending on the setup, and allowed the injection of pure LA when the system was at the desired temperature. Figure 15 presents the GC-EI-MS traces obtained for the products collected in the receiving RBF (a yellow liquid product was observed), for
reactions where the LA was added to the catalyst (ZrO$_2$) in two different manners (i) in the beginning of the process, when both catalyst and LA were heated together; and (ii) when the melted LA was added dropwise after the system reached 350 °C. A constant reflux was being observed and, as a result, a portion of the products that were evaporating were being condensed and collected in the receiving RBF and the other part was returning to the reaction RBF, where further reactions could occur.

![Diagram of reactions](image)

**Figure 15.** GC-EI-MS traces of liquid products for ketonizations of pure LA at 350 °C in a RBF with ZrO$_2$. 

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As can be seen from Figure 15, the reduction of the contact time between the LA and the catalyst did in fact result in the formation of NTO. However, a large portion of LA was unreacted and mainly decomposition products were observed, especially in the reaction where the LA was added and heated at the same time as the catalyst. For this reaction, the products in the RBF where the reaction was taking place was a dark/black viscous liquid, very similar to those observed in the batch reactor. For the reaction where the LA was added dropwise after the system was at 350 ºC, the catalyst also presented evidence of substrate and products decomposing in its surface. The catalyst color changed from white (original state of the ZrO₂) to a brown color during this reaction.

4.5. Ketonizations in a flow reactor

This section will present data obtained in the different setups applied in ketonization reactions of acetic acid, LA and LA ketalts with different catalysts and with varied experimental parameters in a flow reactor designed and built by the author of this thesis. Two different setups for the flow reactor were attempted, with the injection of substrate in the bottom of the reactor tube (upstream), and with the injection of substrate in the top of the reactor tube (downstream). The data analysis will concentrate in the reactions performed in the downstream setup, because they covered more aspects and different experimental parameters. Example GC-EI-MS traces for the reactions performed in the upstream setup can be seen in Appendix C (Figures C2, C3 and C4).

4.5.1. Reactions in a downstream setup

The results presented in this section correspond to the reactions performed in the flow reactor in a downstream setup. Among the data presented, there is a validation for the flow reactor designed applying acetic acid, which is shown to undergo ketonization reactions; reactions of LA in different solvents; aqueous solutions of LA reacted using different catalysts; LA ketal reactions...
and comparisons of different experimental parameters (e.g. substrate flow, Ar flow and temperature). In addition to the GC-EI-MS data, tables are provided comparing residence time and WHSV for the reactions performed.

### 4.5.1.1. Validation of the system with acetic acid

To ensure that the catalyst synthesized (CeO$_2$/Al$_2$O$_3$) and the built flow reactor were operating properly, pure acetic acid, and solutions of acetic acid in solvents (1:2 weight ratio), that would solubilize LA, were injected in the flow reactor for ketonization reactions. These reactions were performed following the procedure presented in the literature.$^{10,25}$ The products of these reactions were analyzed using GC-EI-MS. Figure 16 presents a comparison of the GC-EI-MS traces obtained for these reactions. Table 1 presents the data for residence time and WHSV.

**Table 1.** Residence time and WHSV for the reactions performed with acetic acid.

<table>
<thead>
<tr>
<th>Entry$^a$</th>
<th>Reaction description</th>
<th>Residence time [s]</th>
<th>WHSV [g$<em>{\text{sub}}$·h$^{-1}$/g$</em>{\text{cat}}$]</th>
<th>Catalyst</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$^b$</td>
<td>Acetic acid (pure)</td>
<td>21</td>
<td>1.9</td>
<td>CeO$_2$/Al$_2$O$_3$ 20wt%</td>
</tr>
<tr>
<td>2$^c$</td>
<td>Acetic acid (in different solvents)$^d$</td>
<td>21</td>
<td>0.9</td>
<td>CeO$_2$/Al$_2$O$_3$ 20wt%</td>
</tr>
</tbody>
</table>

$^a$Reaction conditions: ketonizations performed at 400 °C (catalyst zone temperature) in a fixed-bed flow reactor (5 in.), injection point temperature kept at 260 °C, substrate feed rate of 0.150 mL/min and Ar flow of 50 mL/min (30.0 psi feed pressure), ~ 5 g of catalyst was used.

$^b$Pure acetic acid used in the injections. $^c$A solution of 2:1 solvent:acetic acid (weight ratio) prepared using ~ 15g of acetic acid dissolved in 30 mL of solvent. $^d$Solvents being H$_2$O (HPLC grade), methanol, toluene or dioxane.
Figure 16. GC-EI-MS traces for the liquid products of reactions of pure acetic acid and solutions of acetic acid in different organic solvents.
Figure 16 shows that the reactions were well-defined, resulting in the production of acetone as the major product, especially when an aqueous solution of acetic acid was injected. The reactions with toluene presented some side products, but they were also observed in the other reactions. Reactions of acetic acid with methanol and dioxane were also performed. For the reactions with MeOH, no liquid product was observed after 1 h of reaction. The reactions with dioxane resulted in a very complex mixture of products, which discouraged the use of this solvent in reactions with LA.

During all reactions, a white smoke was observed. The composition of the smoke was determined using GC-EI-MS, and the peaks were associated to acetone, unreacted acetic acid and some products that could not be fully identified.

After the reactions, the catalyst turned from pale yellow to a grey color, with some of the pellets in the top of the reactor being completely black. This result demonstrates that the substrate and – in some cases – the solvent is decomposing in the surface of the catalyst.

Considering the data obtained for acetic acid, ketonization reactions were performed in solutions of LA with H₂O, acetone or toluene.

### 4.5.1.2. Ketonization of aqueous solutions of levulinic acid with CeO₂/Al₂O₃

After reactor validation, the ketonization of LA in H₂O was attempted using the fixed-bed flow reactor. The first attempts were performed using a 5 in. reactor tube. For this series of experiments, the goal was to evaluate how the weight ratio of LA:H₂O affected the composition and amount of products obtained. The liquid products of these reactions were analyzed using GC-EI-MS (Figure 17). Table 2 presents the data for residence time and WHSV.
Table 2. Residence time and WHSV comparison for the reactions performed with varying weight ratios of LA:H$_2$O.

<table>
<thead>
<tr>
<th>Entry$^a$</th>
<th>Substrate feed</th>
<th>Residence time [s]</th>
<th>WHSV [g$<em>{sub}$.h$^{-1}$/g$</em>{cat}$]</th>
<th>Catalyst</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$^b$</td>
<td>1:2 (LA:H$_2$O) weight ratio</td>
<td>21</td>
<td>0.9</td>
<td>CeO$_2$/Al$_2$O$_3$ 20wt%</td>
</tr>
<tr>
<td>2$^c$</td>
<td>1:1 (LA:H$_2$O) weight ratio</td>
<td>21</td>
<td>1.8</td>
<td>CeO$_2$/Al$_2$O$_3$ 20wt%</td>
</tr>
<tr>
<td>3$^d$</td>
<td>2:1 (LA:H$_2$O) weight ratio</td>
<td>21</td>
<td>3.6</td>
<td>CeO$_2$/Al$_2$O$_3$ 20wt%</td>
</tr>
</tbody>
</table>

$^a$Reaction conditions: ketonizations performed at 400 ºC (catalyst zone temperature) in a fixed-bed flow reactor (5 in.), injection point temperature kept at 280 ºC, substrate feed rate of 0.150 mL/min and Ar flow of 50 mL/min (30.0 psi feed pressure), ~ 5 g of catalyst was used.

$^b$Aqueous solution containing ~ 15 g of LA and ~ 30 g of H$_2$O (HPLC grade).

$^c$Aqueous solution containing ~ 20 g of LA and ~ 20 g of H$_2$O (HPLC grade).

$^d$Aqueous solution containing ~ 20 g of LA and ~ 10 g of H$_2$O (HPLC grade).
Figure 17. GC-EI-MS traces for the liquid products of reactions of aqueous solutions of LA with varying LA:H₂O weight ratios.
The presence of NTO was negligible for all the ratios tested. However, the decomposition products obtained from NTO were clearly observed in addition to the decomposition products of LA (α-AL and β-AL). The major difference among the different ratios is associated with the physical characteristics of the liquid product being obtained over time. All liquid samples collected throughout reaction 1 were pale yellow, up to 2 h of reaction (the point at which the reaction was stopped). However, when the ratio of LA/H$_2$O was increased, the color and viscosity of the liquid product changed. For reactions 2 and 3, black drops were being observed around 30 and 35 min respectively, this is associated with the higher occurrence of decomposition of substrate and products inside the reactor (Appendix C, Figure C5, for a GC-EI-MS trace of this sample).

Throughout the entire duration of the reaction, a white smoke was again observed and its composition determined using GC-EI-MS. The peaks were identified as α-AL, β-AL, 3-MCP, acetone, unreacted LA and products that could not be identified. The catalyst recovered from the reactions also presented some variations. For the 1:2 weight ratio LA:H$_2$O, the color of the catalyst was brown after 2 h of reaction; on the other hand, for the two other reactions, the catalyst recovered was mostly black or dark brown.

Comparing the results obtained in the flow system with the batch reactor, the decarboxylation of LA to 2-butanone, which was one of the major products in the closed system, is not observed when performing the reactions in flow conditions.

Aiming to identify if the catalyst was causing the decomposition of LA and its products in the flow reactions, ZrO$_2$ was used in reactions instead of the CeO$_2$/Al$_2$O$_3$. The results are presented in the next section.
4.5.1.3. Ketonization of aqueous solutions of levulinic acid applying ZrO$_2$ as a catalyst

Following the attempts of performing the ketonization of LA with CeO$_2$/Al$_2$O$_3$ 20wt%, ZrO$_2$ was used as a catalyst in the same conditions applied for entry 1 of Table 2. In addition, a reaction using ~ 2.5 g of ZrO$_2$ instead of 5 g and with an increased Ar flow was also performed. The goal was to evaluate if a different ketonization catalyst would have more success to produce NTO. The liquid products of the reaction were analyzed using GC-EI-MS, and Figure 18 compares the GC-EI-MS trace to that of the reaction with the CeO$_2$ catalyst. Table 3 presents the data for residence time and WHSV.

Table 3. Residence time and WHSV comparison for the reactions performed with ZrO$_2$ and CeO$_2$/Al$_2$O$_3$.

<table>
<thead>
<tr>
<th>Entry$^a$</th>
<th>Substrate feed</th>
<th>Residence time [s]</th>
<th>WHSV [g$<em>{\text{sub}}$.h$^{-1}$/g$</em>{\text{cat}}$]</th>
<th>Catalyst</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1:2 (LA:H$_2$O) weight ratio</td>
<td>21</td>
<td>0.9</td>
<td>CeO$_2$/Al$_2$O$_3$ 20wt%</td>
</tr>
<tr>
<td>2</td>
<td>1:2 (LA:H$_2$O) weight ratio</td>
<td>21</td>
<td>0.9</td>
<td>ZrO$_2$</td>
</tr>
<tr>
<td>3$^b$</td>
<td>1:2 (LA:H$_2$O) weight ratio</td>
<td>5.2</td>
<td>1.8</td>
<td>ZrO$_2$</td>
</tr>
</tbody>
</table>

$^a$Reaction conditions: ketonizations performed at 400 °C (catalyst zone temperature) in a fixed-bed flow reactor (5 in.), injection point temperature kept at 280 °C, substrate feed rate of 0.150 mL/min and Ar flow of 50 mL/min (30.0 psi feed pressure), with ~ 5 g of catalyst, and an aqueous solution containing ~ 15 g of LA and ~ 30 g of H$_2$O (HPLC grade) was used in the reactions. $^b$For this reaction, ~ 2.5 g of catalyst was used and the Ar flow was increased to 100 mL/min (30.0 psi feed pressure).
Figure 18. GC-EI-MS traces for the liquid products of reactions of aqueous solutions of LA (1:2 weight ratio) with either ZrO$_2$ or CeO$_2$/Al$_2$O$_3$ as catalyst.
As shown in Figure 18, there is no clear distinction between the results obtained for the reaction applying ZrO₂ when compared to the one applying CeO₂/Al₂O₃. Both, the product distribution and intensity in the products are very similar for the two reactions, although the counts for NTO are higher for the reaction with ZrO₂, the GC-EI-MS performed was not quantitative, so we cannot confirm that more NTO was produced. Similar to the reactions described in section 4.5.1.2, throughout the entire duration of the reaction, white smoke was observed. The composition of the smoke was also analogous to the one previously described. The major difference was observed in the physical aspects of the liquid products obtained throughout each reaction. As previously mentioned, for the reaction with CeO₂/Al₂O₃ the liquid product was pale-yellow up to 2 h of reaction. On the other hand, after 50 min of the reaction with ZrO₂, black viscous drops were observed, and production of the viscous black liquid was constant after that point. The color of the catalyst recovered (black pellets) at the end of the reaction was also impacted by the decomposition reactions taking place in the reactor.

Considering that changing the catalyst did not promote a clear improvement in the production of NTO, the catalyst load was reduced, the Ar flow increased, and a reaction with fresh catalyst was performed in order to evaluate the impact of a shorter residence time. Figure 19 presents a comparison between the 2 reactions performed using ZrO₂ as catalyst.
Figure 19. GC-EI-MS traces for the liquid products of reactions of aqueous solutions of LA (1:2 weight ratio) with varying loads of ZrO₂ and carrier gas flow.
The variation in the catalyst load did not promote any significant variation in the products obtained in the ketonization reaction of LA. The shorter contact time (5 s instead of 21 s) did not significantly impact the final products, with the only clear change being the physical qualities of the solution obtained at the end of the reactions. For the reaction with higher Ar flow rate and smaller amount of catalyst, no black viscous product was observed after 2 h of reaction, the liquid product remained yellow.

4.5.1.4. Ketonization of levulinic acid dissolved in different organic solvents

Solubility tests were performed using LA and different organic solvents. This substrate was found to be soluble in acetone, toluene, MeOH and dioxane and insoluble in cyclohexane. Considering the results obtained in the solubility tests and the results obtained in reactions of acetic acid in those organic solvents, ketonizations of LA were performed using toluene and acetone as solvent. Table 4 compares the results obtained when using water versus toluene as solvent, and the GC-EI-MS traces are presented in Figure 20.

Table 4. Residence time and WHSV comparison for the reactions performed with either aqueous solution of LA or a toluene-LA solution.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate feed</th>
<th>Residence time [s]</th>
<th>WHSV [g_{sub-h^{-1}}/g_{cat}]</th>
<th>Catalyst</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1:2 (LA:H₂O) weight ratio</td>
<td>10</td>
<td>1.5</td>
<td>CeO₂/Al₂O₃ 20wt%</td>
</tr>
<tr>
<td>2ᵇ</td>
<td>1:2 (LA:toluene) weight ratio</td>
<td>10</td>
<td>1.5</td>
<td>CeO₂/Al₂O₃ 20wt%</td>
</tr>
</tbody>
</table>

ᵃReaction conditions: ketonizations performed at 400 ºC (catalyst zone temperature) in a fixed-bed flow reactor (5 in.), injection point temperature kept at 280 ºC, substrate feed rate of 0.250 mL/min and Ar flow of 100 mL/min (30.0 psi feed pressure), with ~ 5 g of catalyst, and an aqueous solution containing ~ 7.5 g of LA and ~ 15 g of H₂O (HPLC grade) was used in the reactions.ᵇFor this reaction, instead of an aqueous solution of LA, a toluene solution of LA was used in the ketonization, applying ~ 7.5 g of LA and ~ 15 g of toluene.
Figure 20. GC-EI-MS traces for the liquid products of reactions performed on aqueous solutions of LA or toluene with LA solution applying CeO$_2$/Al$_2$O$_3$ as catalyst.
As can be observed, the reaction with toluene had a very similar product distribution to the one with water. However, as the GC-EI-MS trace shows, some products which were not observed before are present when toluene is the solvent. Some of these products have high m/z ratios, which suggests that they might result of reaction between the solvent and the substrate or products.

The GC-EI-MS trace does not present a full picture of the reaction. During the reaction with toluene, the liquid production suffered many interruptions in its flow due to decomposition of the products inside of the reactor, at some points, the Ar flow completely stopped for some seconds. The interruptions in the flow of products and gas, were accompanied by the observation of viscous black drops and an excessive amount of the white smoke. The catalyst recovered at the end of the reaction was completely black.

Following the unsatisfactory results obtained after the reactions performed with toluene, solutions of LA in acetone were used in injections in the fixed-bed flow reactor. For this solvent, a temperature and an Ar flow series were performed. The data for residence time and WHSV can be seen on Table 5 and the GC-EI-MS traces are plotted in Figures 21 and 22.
Table 5. Residence time and WHSV comparison for the reactions performed with varying temperatures or Ar flow of LA:acetone solutions.

<table>
<thead>
<tr>
<th>Entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Reaction description</th>
<th>Residence time [s]</th>
<th>WHSV [g&lt;sub&gt;sub&lt;/sub&gt;::h&lt;sup&gt;-1&lt;/sup&gt;/g&lt;sub&gt;cat&lt;/sub&gt;]</th>
<th>Catalyst</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1&lt;sup&gt;b&lt;/sup&gt;</strong></td>
<td>LA:acetone at 300 ºC</td>
<td>21</td>
<td>0.9</td>
<td>CeO&lt;sub&gt;2&lt;/sub&gt;/Al&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt; 20wt%</td>
</tr>
<tr>
<td><strong>2&lt;sup&gt;c&lt;/sup&gt;</strong></td>
<td>LA:acetone at 350 ºC</td>
<td>21</td>
<td>0.9</td>
<td>CeO&lt;sub&gt;2&lt;/sub&gt;/Al&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt; 20wt%</td>
</tr>
<tr>
<td><strong>3&lt;sup&gt;d&lt;/sup&gt;</strong></td>
<td>LA:acetone at 400 ºC</td>
<td>21</td>
<td>0.9</td>
<td>CeO&lt;sub&gt;2&lt;/sub&gt;/Al&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt; 20wt%</td>
</tr>
<tr>
<td><strong>4&lt;sup&gt;e&lt;/sup&gt;</strong></td>
<td>LA:acetone with Ar flow of 100 mL/min</td>
<td>10</td>
<td>0.9</td>
<td>CeO&lt;sub&gt;2&lt;/sub&gt;/Al&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt; 20wt%</td>
</tr>
<tr>
<td><strong>5&lt;sup&gt;f&lt;/sup&gt;</strong></td>
<td>LA:acetone with Ar flow of 150 mL/min</td>
<td>7</td>
<td>0.9</td>
<td>CeO&lt;sub&gt;2&lt;/sub&gt;/Al&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt; 20wt%</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reaction conditions: ketonizations performed in a fixed-bed flow reactor (5 in.), injection point temperature kept at 260 ºC, substrate feed rate of 0.150 mL/min, ~ 5 g of catalyst were used, and a solution of LA with acetone containing ~ 15 g of LA and ~ 30 mL of acetone was used in the reactions. <sup>b</sup>For this reaction, the temperature in the catalyst zone was 300 ºC and the Ar flow was 50 mL/min (30.0 psi feed pressure). <sup>c</sup>For this reaction, the temperature in the catalyst zone was 350 ºC and the Ar flow was 50 mL/min (30.0 psi feed pressure). <sup>d</sup>For this reaction, the temperature in the catalyst zone was 400 ºC and the Ar flow was 50 mL/min (30.0 psi feed pressure). <sup>e</sup>For this reaction, the temperature in the catalyst zone was 400 ºC and the Ar flow was 100 mL/min (30.0 psi feed pressure). <sup>f</sup>For this reaction, the temperature in the catalyst zone was 400 ºC and the Ar flow was 150 mL/min (30.0 psi feed pressure).
Figure 21. GC-EI-MS traces of liquid products for ketonizations of LA:acetone solutions with temperatures varying from 300 to 400 °C with the catalyst CeO$_2$/Al$_2$O$_3$ 20wt%.
Figure 22. GC-EI-MS traces of liquid products for ketonizations of LA:acetone solutions with Ar flow varying from 50 to 150 mL/min with the catalyst CeO$_2$/Al$_2$O$_3$ 20wt%.
All the reactions performed with acetone resulted in a liquid product with a very complex mixture of products. Most of them could not be determined, as they are most likely the result of reactions between the solvent and the substrate, as well as products being generated in the catalyst bed.

For the reactions performed with varying temperatures, the liquid color and characteristics changed with the increase in temperature. The liquid product changed from a yellow color (300 ºC) to an orange color (350 ºC) and at 400 ºC the black viscous product was observed in larger quantities. The color of the catalyst recovered after the reactions also changed with the increase in temperature, varying from a brown color for 300 ºC to a black color for the reaction performed at 400 ºC.

For the reactions where the Ar flow was altered, the samples obtained for all the experiments were very similar. The liquid had a dark orange color and the catalyst was dark brown/black at the end of the reactions.

Considering that the reactions with toluene and acetone resulted in a complex product mixture, and NTO was not observed as one of these products, H₂O was maintained as the solvent for the reactions carried out in the shorter reactor with a smaller catalyst load.

4.5.1.5. Ketonization of aqueous solutions of levulinic acid applying a shorter reactor (2.5” reactor)

Thus far, most of the experimental parameters that could be manipulated to achieve a satisfactory ketonization of LA were tested. Combining the reaction conditions that resulted in any production of NTO lead to the decision of perform a final set of reactions before attempting the preparation of the LA cyclic ketals.
For these reactions, instead of using the 5 in. reactor tube, a 2.5 in. reactor tube was used, the catalyst load was decreased to \( \sim 2.5 \) g, water was selected as solvent and a 1:1 weight ratio of water to LA was used. The parameters analyzed were: (i) the Ar flow rate, which allows the manipulation of residence time; (ii) the substrate feed rate, which directly impacts the WHSV; and (iii) the temperature at which the reactions were performed.

Table 6 and Figure 23 provide the parameters and results obtained for the reactions performed with varying Ar flow.

**Table 6.** Residence time and WHSV comparison for the ketonizations reactions performed with varying Ar flow using a 1:1 weight ratio of LA:H\(_2\)O and CeO\(_2\)/Al\(_2\)O\(_3\) as catalyst.

<table>
<thead>
<tr>
<th>Entry(^a)</th>
<th>Reaction description</th>
<th>Residence time [s]</th>
<th>WHSV ( [g_{\text{sub}}\cdot\text{h}^{-1}/g_{\text{cat}}] )</th>
<th>Catalyst</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^b)</td>
<td>LA:H(_2)O with Ar flow of 50 mL/min</td>
<td>10.4</td>
<td>3.6</td>
<td>CeO(_2)/Al(_2)O(_3) 20wt%</td>
</tr>
<tr>
<td>2(^c)</td>
<td>LA:H(_2)O with Ar flow of 100 mL/min</td>
<td>5.2</td>
<td>3.6</td>
<td>CeO(_2)/Al(_2)O(_3) 20wt%</td>
</tr>
<tr>
<td>3(^d)</td>
<td>LA:H(_2)O with Ar flow of 150 mL/min</td>
<td>3.5</td>
<td>3.6</td>
<td>CeO(_2)/Al(_2)O(_3) 20wt%</td>
</tr>
</tbody>
</table>

\(^a\)Reaction conditions: ketonizations performed at 400 °C (catalyst zone temperature) in a fixed-bed flow reactor (2.5 in.), injection point temperature kept at 280 °C, substrate feed rate of 0.150 mL/min, \( \sim 2.5 \) g of catalyst was used, and the reactions were performed to a 1:1 weight ratio aqueous solution of LA containing \( \sim 20 \) g of LA and \( \sim 20 \) g of H\(_2\)O (HPLC grade). \(^b\)Ar flow of 50 mL/min (30.0 psi feed pressure). \(^c\)Ar flow of 100 mL/min (30.0 psi feed pressure). \(^d\)Ar flow of 150 mL/min (30.0 psi feed pressure).
Figure 23. GC-EI-MS traces of liquid products for ketonizations of LA:H₂O solutions with Ar flow varying from 50 to 150 mL/min with the catalyst CeO₂/Al₂O₃ 20wt%.
The product composition was not considerably affected by the variations in the Ar flow rate. NTO was observed, but not in appreciable amounts. The physical appearance of the liquid products and the catalyst recovered from the reactor changed accordingly with the changes in the flow rate. The reaction with lower Ar flow rate produced the black viscous liquid before the other two reactions, around 11 min in comparison to 16 min for the other 2 runs. The catalyst was very similar for both the reactions in entries 2 and 3 on Table 6, having a brown color at the end of the reaction, while the catalyst recovered after the reaction for entry 1 was a mixture of dark brown and black pellets.

Although the data obtained from the GC-EI-MS is not quantitative, the samples used to obtain the traces for entries 2 and 3 were collected around the same time, and the volume injected was also very similar. Taking that into consideration, GC-EI-MS traces show that the amount of unreacted LA is smaller for entry 2 than for entry 3, so this Ar flow could result in better results with variations in the other experimental parameters. Considering the results obtained, for the series where the feed flow rate was varied, the Ar flow rate used was 100 mL/min.

Table 7 and Figure 24 provide the parameters and results obtained for the reactions performed with varying substrate feed flow rate.
Table 7. Residence time and WHSV comparison for the ketonizations reactions performed with varying feed flow using a 1:1 weight ratio of LA:H₂O and CeO₂/Al₂O₃ as catalyst.

<table>
<thead>
<tr>
<th>Entryᵃ</th>
<th>Reaction description</th>
<th>Residence time [s]</th>
<th>WHSV [gₘₜₚ⁻¹·h⁻¹/gcat]</th>
<th>Catalyst</th>
</tr>
</thead>
<tbody>
<tr>
<td>1ᵇ</td>
<td>LA:H₂O feed of 0.075 mL/min</td>
<td>5.2</td>
<td>1.8</td>
<td>CeO₂/Al₂O₃ 20wt%</td>
</tr>
<tr>
<td>2ᶜ</td>
<td>LA:H₂O feed of 0.150 mL/min</td>
<td>5.2</td>
<td>3.6</td>
<td>CeO₂/Al₂O₃ 20wt%</td>
</tr>
<tr>
<td>3ᵈ</td>
<td>LA:H₂O feed of 0.300 mL/min</td>
<td>5.2</td>
<td>7.2</td>
<td>CeO₂/Al₂O₃ 20wt%</td>
</tr>
</tbody>
</table>

ᵃReaction conditions: ketonizations performed at 400 °C (catalyst zone temperature) in a fixed-bed flow reactor (2.5 in.), injection point temperature kept at 280 °C, Ar flow of 100 mL/min (30.0 psi feed pressure), ~2.5 g of catalyst was used, and the reactions were performed to a 1:1 weight ratio aqueous solution of LA containing ~20 g of LA and ~20 g of H₂O (HPLC grade).ᵇFeed rate of 0.075 mL/min.ᶜFeed rate of 0.150 mL/min.ᵈFeed rate of 0.300 mL/min.
Figure 24. GC-EI-MS traces of liquid products for ketonizations of LA:H₂O solutions with feed flow rate varying from 0.075 to 0.300 mL/min with the catalyst CeO₂/Al₂O₃ 20wt%.
As Figure 24 shows, the product distribution is again very similar for the reactions performed with varying feed flow rate. The production of NTO was negligible. Following what was expected, the production of the viscous black liquid was retarded in the reaction carried out with the 0.075 mL/min feed rate. The catalyst recovered after the reaction also had pellets less dark when compared to the pellets recovered for the reactions in entries 2 and 3 of Table 7. The reaction carried out with a 0.300 mL/min feed rate took only 4 min to start producing the viscous black liquid. As a result, the feed rate of 0.075 mL/min was selected to perform the series where the temperature was varied.

Table 8 and Figure 25 provide the parameters and results obtained for the reactions performed with varying reaction temperature.

**Table 8.** Residence time and WHSV comparison for the ketonizations reactions performed with varying temperatures using a 1:1 weight ratio of LA:H$_2$O and CeO$_2$/Al$_2$O$_3$ as catalyst.

<table>
<thead>
<tr>
<th>Entry$^a$</th>
<th>Reaction description</th>
<th>Residence time [s]</th>
<th>WHSV [g$<em>{sub}$.h$^{-1}$/g$</em>{cat}$]</th>
<th>Catalyst</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$^b$</td>
<td>LA:H$_2$O reacting at 300 ºC</td>
<td>5.2</td>
<td>1.8</td>
<td>CeO$_2$/Al$_2$O$_3$ 20wt%</td>
</tr>
<tr>
<td>2$^c$</td>
<td>LA:H$_2$O reacting at 350 ºC</td>
<td>5.2</td>
<td>1.8</td>
<td>CeO$_2$/Al$_2$O$_3$ 20wt%</td>
</tr>
<tr>
<td>3$^d$</td>
<td>LA:H$_2$O reacting at 400 ºC</td>
<td>5.2</td>
<td>1.8</td>
<td>CeO$_2$/Al$_2$O$_3$ 20wt%</td>
</tr>
</tbody>
</table>

$^a$Reaction conditions: ketonizations performed in a fixed-bed flow reactor (2.5 in.), injection point temperature keep at 280 ºC, substrate feed rate of 0.075 mL/min, ~ 2.5 g of catalyst was used, Ar flow of 100 mL/min (30.0 psi feed pressure), and the reactions were performed to a 1:1 weight ratio aqueous solution of LA containing ~ 20 g of LA and ~ 20 g of H$_2$O (HPLC grade). $^b$Temperature in the catalyst bed of 300 ºC. $^c$Temperature in the catalyst bed of 350 ºC. $^d$Temperature in the catalyst bed of 400 ºC.
Figure 25. GC-EI-MS traces of liquid products for ketonizations of LA: H₂O solutions with the temperature varying from 300 to 400 °C with the catalyst CeO₂/Al₂O₃ 20wt%.
The same products were observed in all of the reactions, independent of the temperature applied. However, as evidenced in the GC-EI-MS traces, the products are less prominent in the reactions at lower temperatures, and the amount of unreacted LA is also higher; though it is important to mention that the analyses were not quantitative, so the observations are only qualitative.

Regarding the color of the liquid products obtained at the end of the reactions, the samples from entries 1 and 2 on Table 8 did not contain any black viscous drops up to 60 min of reaction. The recovered catalyst for both samples was also very similar and consisted of a mixture of light brown pellets and some black pellets, especially the pellets close to the injection point.

Although the reactions described in this section were performed applying the best reaction conditions obtained throughout this project, the production of NTO was unsatisfactorily low. As a result, the preparation and ketonization of LA cyclic ketals were attempted in order to evaluate if the protection of the ketone functionality in the LA molecule could result in better production of NTO.

4.5.1.6. Ketonization applying protected levulinic acid

The preparation of the LA ketals followed literature procedures and is described in detail in the Experimental section.79 The formation of LACEA was confirmed by NMR and GC-EI-MS, while the production of LACEAHE was confirmed by GC-EI-MS (Appendix B, Figures B4 and B5 and Appendix C, Figure C6, for data). Both compounds were transparent viscous liquids at room temperature.

For the synthesis of LACEA, a small amount of benzene was observed both in the NMR and the GC-EI-MS traces. In addition, the GC-EI-MS traces showed a negligible amount of LA, and small amounts of the LACEAHE that were not converted to LACEA during the preparation of the
compound. For the synthesis of LACEAHE, the GC-EI-MS traces showed the presence of benzene and small amounts of levulinaldehyde ethylene ketal (LAEK).

Flow reactions applying the downstream setup were performed on pure LACEA, dibutyl ether solutions of LACEA (1:1 in volume) and pure LACEAHE. The results are presented below.

4.5.1.6.1. Levulinic acid cyclic ethylene acetal (LACEA)

Table 9 and Figure 26 present the data obtained for the ketonization reactions applying LACEA as a substrate. The comparison is made between injections with pure LACEA and a 1:1 volume ratio dibutyl ether solution of LACEA.

Table 9. Residence time and WHSV comparison for the ketonizations reactions performed with pure LACEA and a dibutyl ether solution of LACEA applying CeO$_2$/Al$_2$O$_3$ as catalyst.

<table>
<thead>
<tr>
<th>Entry$^a$</th>
<th>Reaction description</th>
<th>Residence time [s]</th>
<th>WHSV $[\text{g}<em>{\text{sub}}.\text{h}^{-1}/\text{g}</em>{\text{cat}}]$</th>
<th>Catalyst</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$^b$</td>
<td>Pure LACEA</td>
<td>10.4</td>
<td>2.1</td>
<td>CeO$_2$/Al$_2$O$_3$ 20wt%</td>
</tr>
<tr>
<td>2$^c$</td>
<td>Dibutyl ether sol of LACEA (1:1 in vol)</td>
<td>10.4</td>
<td>2.2</td>
<td>CeO$_2$/Al$_2$O$_3$ 20wt%</td>
</tr>
</tbody>
</table>

$^a$Reaction conditions: ketonizations performed at 400 °C (catalyst zone temperature) in a fixed-bed flow reactor (5 in.), injection point temperature kept at 280 °C, substrate feed rate of 0.150 mL/min and Ar flow of 100 mL/min (30.0 psi feed pressure), ~ 5 g of catalyst was used. $^b$Pure LACEA was applied in the injections. $^c$A dibutyl ether (~ 15 mL) solution of LACEA (~ 17 g) was used in the injections.
Figure 26. GC-EI-MS traces for the liquid products of reactions performed with pure LACEA and dibutyl ether solutions of LACEA applying CeO$_2$/Al$_2$O$_3$ as catalyst.
The reactions of LACEA resulted in the formation of the same products obtained for the reactions with LA, but products with larger m/z ratios were also observed. The protecting group was also removed during the reactions, as can be evidenced by the presence of LA; however, the amount of unreacted LACEA was marginal. No form of NTO – either with or without protecting groups in the original ketone position – was observed. The major difference between the reactions with LACEA in comparison to LA reactions was the nature of the liquid products obtained.

The reaction with the dibutyl ether solution of LACEA resulted in the formation of 2 distinct liquid phases, which were analysed separately by GC-EI-MS (Figure 26). The lower density layer contained the solvents that were present due to the synthesis of LACEA and had a yellow color. The high-density liquid phase was more viscous, had a black color, and was not soluble in dibutyl ether. In addition, for the first time, the quartz wool used to keep the catalyst in place inside of the reactor tube was brown and impregnated with reaction products. The catalyst recovered at the end of this reaction was also very dark and the reactor body was also impregnated with reaction products.

The reaction applying pure LACEA had only one phase, which presented physical characteristics very similar to the ones observed for the high-density product observed in the reactions with dibutyl ether. The liquid products had only one phase and a black color. The catalyst recovered, and the quartz wool were black and impregnated with reaction products.

A final reaction was attempted, this time instead of applying LACEA, LACEAHE was used. This molecule, which can be isolated as an intermediate product obtained in the process of production of LACEA, has an ester functionality instead of a carboxylic acid (Scheme 12).
4.5.1.6.2. Levlulinic acid cyclic ethylene acetal hydroxyethyl ester (LACEAHE)

The reaction with LACEAHE as a substrate was performed. Table 10 and Figure 27 present a comparison between the data obtained for the ketonization reactions with LACEA and LACEAHE.

Table 10. Residence time and WHSV comparison for the ketonizations reactions performed with pure LACEAHE and pure LACEA applying CeO$_2$/Al$_2$O$_3$ as catalyst.

<table>
<thead>
<tr>
<th>Entry$^a$</th>
<th>Reaction description</th>
<th>Residence time [s]</th>
<th>WHSV [g$<em>{sub}.h^{-1}$/g$</em>{cat}$]</th>
<th>Catalyst</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$^b$</td>
<td>LACEA</td>
<td>10.4</td>
<td>2.1</td>
<td>CeO$_2$/Al$_2$O$_3$ 20wt%</td>
</tr>
<tr>
<td>2$^c$</td>
<td>LACEAHE</td>
<td>10.4</td>
<td>1.8$^d$</td>
<td>CeO$_2$/Al$_2$O$_3$ 20wt%</td>
</tr>
</tbody>
</table>

$^a$Reaction conditions: ketonizations performed at 400 ºC (catalyst zone temperature) in a fixed-bed flow reactor (5 in.), injection point temperature kept at 280 ºC, substrate feed rate of 0.150 mL/min and Ar flow of 100 mL/min (30.0 psi feed pressure), ~ 5 g of catalyst was used.
$^b$Pure LACEA was applied in the injections. $^c$Pure LACEAHE was used in the injections. $^d$Values for the density of LACEAHE are not available, as a result, the WHSV for this substrate was obtained considering a density of 1.0 g/mL.
Figure 27. GC-EI-MS traces for the liquid products of reactions performed with pure LACEAHE and pure LACEA applying CeO$_2$/Al$_2$O$_3$ as catalyst.
As Figure 27 shows, most of the LACEAHE substrate remained unreacted. The substrate was deprotected during the ketonization reaction – LA was not present in the sample before the reaction – and LA reacted producing α-AL and β-AL, and NTO was completely decomposed to 3-MCP and possibly humins. The liquid product obtained at the end of this reaction had similar physical characteristics to the one obtained after the ketonization reaction of LACEA. It was dark brown and viscous. The reactor appearance was also similar, as the products of the reaction completely impregnated the catalyst (which had a dark brown color after the reaction), the quartz wool and the reactor body.
5. Discussion

This section analyzes and interprets in depth the main findings obtained from applying a batch reactor and the fixed-bed flow reactor which was designed and built to perform the ketonic decarboxylation of LA and LA ketals.

5.1. Thermochemical map for the ketonization of levulinic acid

As can be observed in the thermochemical map (Figure 7), NTO is among the most thermodynamically favorable products. However, the simple decarboxylation of LA is more favorable, accompanied by the aldol condensation of NTO followed by a dehydration, with 3-MCP being the most thermodynamically favorable product. Even though the aldol condensation required for the formation of 3-MCP is thermodynamically unfavorable when starting from NTO, if a catalyst – e.g. acidic or basic sites on the catalyst surface – decreases the activation barrier for the formation of the aldol product, 3-MCP will be formed, as it is the thermodynamic sink for this set of reactions. As can be seen in the thermochemical map, this reaction also requires H₂. Although the system does not have any added hydrogen gas, the decomposition of the substrate and eventual products on the surface of the catalyst (coke formation) could generate the necessary H atoms to perform the hydrogenolysis that produces 3-MCP.

The data obtained from the thermochemical map highlight some of the challenges that needed to be overcome when designing and conducting experiments/reactions. The most important aspect was to stop the reaction at NTO, preventing further self-reactivity of this product which results in 3-MCP. In addition, the catalysts chosen for the reactions had to be more selective towards ketonization reactions in comparison to the decarboxylation of LA. Unfortunately, none of these aspects are accounted for in the calculations that were performed for the thermochemical map. As
a result, the data could only be used to support the hypothesis that NTO could be obtained from LA in a thermodynamically favorable fashion.

As will be presented later, the catalyst and the residence time of the molecules in the reactor played an important role. The catalysts applied are shown to be more selective for the ketonization in comparison to the decarboxylation; however, the contact of the LA molecules with the solid catalytic surface also promoted excessive formation of side products. These include but are not limited to α-AL and β-AL, decomposition of the substrate and products on the catalyst surface (coke), and further reactivity of NTO producing 3-MCP, which was corroborated due to the presence of an acetone peak in the GC-EI-MS traces.

5.2. Catalyst characterization: X-ray powder diffraction (XRD)

The XRD data obtained for the Al₂O₃ support was not matched with only one phase of alumina and, the sample actually had elements that are typically found in different phases of this oxide. The occurrence of such phenomena is contrary to what is expected. The goal of the pre-treatment performed in the alumina was to make the support uniform in case different sources of alumina were applied; this is especially important considering that common environmental aspects – such as humidity and temperature – affect the water content of alumina. At this point, we are not able to pinpoint how such variations would affect the activity of the catalyst towards ketonization reactions. Alumina has a very small activity towards ketonizations, so even if the phases in the alumina used were not clearly identified by XRD, the impact of this change on catalyst activity is believed to be minimal. In addition, the samples were analyzed many months after their synthesis, which could also have caused aging of the support resulting in the presence of multiple phases.
Regarding the results obtained for the CeO$_2$/Al$_2$O$_3$ catalyst, the data obtained is satisfactory. The confirmation that the CeO$_2$ was formed corroborates the experimental operations performed to produce this catalyst. In addition, the observation of the CeO$_2$, not only on the exterior surface of the support, but also in the pores, was one of the goals of the impregnation technique applied. The ketonization reaction is a surface reaction and having CeO$_2$ on the surface and in the pores of the support improves the surface area that is active for the ketonization of carboxylic acids. Unfortunately, as confirmed by the results obtained for the catalyst after being used on ketonization reactions, the additional sites in the pores of the support were also responsible for decomposition reactions of both substrate and products. The black color on the interior of the catalyst confirms the capacity of the molecules to reach the pores, but some of them might get trapped and decompose.

Although the entire surface – including the pores of the catalyst – were covered by decomposition products, only small variations in intensity of the peaks were observed in the XRD patterns for the catalyst before and after the ketonization reactions. This is a positive result suggesting that thermal reactivation could result in regeneration of activity for catalysts that were applied in ketonizations. Unfortunately, when the reactions are taking place inside of the reactor, decomposition of any sort on the surface of the catalyst completely blocks the sites that could be used in the ketonization of the LA molecules. This decomposition is most likely happening concurrently to the ketonization, as can be observed in the GC-EI-MS data.

The interaction between the substrate and catalyst surface is the most fundamental aspect in the ketonization reactions and at the same time is the hardest to control from an experimental standpoint. We are only able to manipulate macroscopic parameters of the reaction, but
interactions such as the one between substrate and catalyst take place at a molecular, or even atomic level and unfortunately cannot be fully controlled by macroscopic manipulations.

5.3. **Ketonizations in batch reactor**

As can be observed in Figure 3, ketonizations tend to be exergonic processes.\textsuperscript{10,67} Analyzing the data obtained for the evolution of pressure and temperature over time presented on Figure 8, the only event that can clearly be observed is the vaporization of LA, which takes place around 245 °C. This could be considered as evidence that no reaction has happened before the LA was in the gaseous state, or that the substrate is decomposing on the surface of the catalyst producing coke; the increase in the pressure is attributed to both the vaporization of LA and the production of decomposition products such as CO\(_2\) (Scheme 11). The major evidence for the production of CO\(_2\) is the pressure observed on the reactor after the reaction was completed and cooled down to room temperature, which varied from 20 to 100 psi depending on the temperature of the reaction. In addition, the pressure stabilized after the reactor reached the desired temperature and, as evidenced by the data presented at 400 °C (Figure 10). This might be an indication that the reactions happening took place during the heat-up, and no further reaction was observed during the hour in which the reactor remained at the final temperature. However, the experimental batch setup applied does not allow to confirm such reactivity patterns.

As can be seen, the contact time between the catalyst and the reaction solution is long, due to the nature of the apparatus. This is an important parameter, because such a long contact time favors the formation of humins as a result of uncontrolled side reactions, resulting in a wide range of undesirable products. The conversion of these products to coke; the coke taking the form of a black product stuck in the bottom of the reactor and on the surface of the catalyst, which can lead to
complete catalyst deactivation over time. In addition, ketonizations are the result of interactions between the substrate in the gas phase with the solid surface of the catalyst. The batch reactor setup is not able to ensure that only LA molecules in the gas phase will interact with the catalyst, in fact, most of the substrate remains in the liquid phase during a large portion of the reaction. Thus, promoting uncontrollable reactivity on the surface of the catalyst, preventing effective interactions of LA molecules in the gas phase with the catalyst.

The same observations can be extended for the reaction performed with RM as a catalyst. Even though the reaction was carried out at lower temperatures (200 °C), the result observed in the GC-EI-MS traces was a complex mixture of products that could not be completely identified. Comparing the results obtained by Schlaf et al.\textsuperscript{36} with the results obtained herein, the presence of H\textsubscript{2} in the reactions performed by Schlaf et al. seems to play a crucial role; the formation of NTO was not observed for reactions carried out in this thesis, and that was the only experimental parameter that was altered. The role played by the H\textsubscript{2} gas is not clear, especially considering the literature for ketonizations, which demonstrated that the carrier gas in flow reactions did not impact the distribution and yield of ketonization products.\textsuperscript{39} The presence of H\textsubscript{2} in the system might protect the substrate from further reacting or decomposing on the surface of the catalyst, but a clear conclusion cannot be drawn without an in-depth theoretical study comparing ketonizations happening under a H\textsubscript{2} or in a N\textsubscript{2} atmosphere in batch conditions, which was beyond the scope of this project.

Only the aqueous solution products present on the top of the humins inside the reactor (solid black products in the bottom of the reactor) could be meaningfully analyzed, using injections on the GC-EI-MS. These samples are most likely composed of water produced during the reactions taking place inside of the reactor, with a small amount of the possible products dissolved in it. The
composition of the final product is more complex than the GC-EI-MS traces can express, and the bulk of the products reside in the complex viscous black liquid which was observed in the bottom of the reactor. This viscous product cannot be properly analyzed or have a proper extraction treatment due to its complex composition. Some attempts were made towards diluting a small fraction of this product in organic solvents such as CH₂Cl₂ and carrying out injections in the GC-EI-MS (Appendix C, Figure C5, for results); however, no meaningful data was obtained. This could be due to the fact that these products are the result of humin formation, and do not possess an appreciable vapor pressure required for GC-type analysis.

Finally, this suggests that due to the elevated contact time, NTO and any other products, as well as the substrate, are further reacting and uncontrollably polymerizing inside of the reactor or being decomposed. Although the batch reactions did not result in the formation of the desired product, the data collected was important to explore and confirm the importance of parameters – such as contact time – which play an important role in the ketonization of LA.

5.4. Ketonization in a RBF system

Figure 15 clearly shows how the ketonization reactions of LA were improved with reductions in contact time. The presence of NTO is a result that corroborates the hypothesis that longer contact time between the reaction solution with the catalyst surface only favors further decomposition, resulting in humins. The RBF system was an improvement in comparison to the batch system, specially because it allowed the direct injection of pure substrate to the system at the reaction temperature; however, this system has its drawbacks.

Due to the use of a RBF made of borosilicate glass, the maximum temperature that the system could be heated to was limited. This could be overcome by replacing the borosilicate RBF with a
quartz RBF which would be able to withstand higher temperatures. The second issue with this system is the fact that even though the contact time was decreased, when LA and catalyst are added at the same time in the beginning of the process, the system takes at least 35 min to reach 350 °C, and after 5 min at this temperature, the liquid begins changing to a black viscous product, which indicates the decomposition of the reaction mixture. Finally, even when the LA is directly injected to the system when the final temperature was already achieved, the vapor products reflux before reaching the condenser and undergo further reactions. The reflux was more appreciable when the LA was added in the beginning of the reaction, resulting in further decomposition of possible liquid products.

In addition to the aspects previously discussed, there is a large quantity of unreacted LA as the data presented on the GC-EI-MS traces demonstrates. This is most likely the result of evaporation of the substrate before any reaction is taking place. The RBF is an open system and there is no way to ensure that the molecules of LA in the gas phase will react on the surface of the solid catalyst, especially when there is still LA in the liquid phase. As evidenced by the previous studies exploring ketonizations, the substrate is always reacting with the catalyst in the gas phase, producing a gas-solid interface and reaction. The RBF system, similar to the batch reactor, is not able to ensure that only molecules in the gas phase interact with the catalyst surface. An exclusive gas-solid interaction could improve the ketonization of the substrate and reduce the occurrence of additional reactions. Our solution to achieve very short contact times and favour a gas-solid interaction between substrate and catalyst was to use a flow system, these systems are what are typically applied for ketonization reactions.
5.5. Ketonizations in a flow reactor

This section will discuss the results obtained in the different setups applied in ketonization reactions of LA and other substrates with different catalysts and with varied experimental parameters in a flow reactor designed and built in-house.

5.5.1. Reactions in a downstream setup

5.5.1.1. Validation of the system with acetic acid

Considering that the major reason for performing reactions in a flow system was to reduce the contact time of the substrate with the catalyst, the results obtained from the reactions of acetic acid were satisfactory. The residence time of the substrate was reduced from a minimum of 35 minutes, when the reactions were performed in the RBF system, to 21 seconds in the flow system. This shorter contact time could reduce the occurrence of side reactions; however, the results with acetic acid cannot be fully extrapolated to LA due to the nature of the substrate and the possible side reactions.

The results obtained in the experiments performed with acetic acid confirm the capability of the catalyst and the reactor to perform ketonizations. The conversion of acetic acid to acetone – the ketonization product of the reaction – was near quantitative. The presence of side products, resulting from reactions of substrate and acetone with the solvent, is a drawback, especially when considering the more complex nature of LA. On the other hand, the results obtained when starting from aqueous solutions of acetic acid are exciting as the reaction presented only a small amount of side products. As previously mentioned, H₂O is a side product of the ketonization reaction; however, its presence as a solvent did not compromise the formation of acetone. As a result, using H₂O with LA could have a good synergy, if the water did not affect the ketonization of LA and, at
the same time, reduce the side reactions of LA, e.g. aldol condensations, that generate water as a by-product. In addition, water is an extremely desirable solvent when working with biomass. Besides being a cleaner solvent, when considering the environmental footprint of water when compared to toluene or acetone, water is also present in most reactions taking place with biomass.

The data obtained with acetic acid also points towards the use of acetone as a solvent in ketonization reactions of LA. As the GC-EI-MS data shows, acetone is very stable at the conditions in which ketonizations are performed and, as a result, in the case that H$_2$O and toluene are not satisfactory solvents for the ketonization of LA, we hypothesized that acetone could be used as a solvent.

### 5.5.1.2. Ketonization of aqueous solutions of levulinic acid with CeO$_2$/Al$_2$O$_3$

As discussed in the previous section (5.4.1.1), the presence of H$_2$O in the system did not compromise the production of acetone when acetic acid was applied in ketonizations. Reactions were then performed with aqueous solutions of LA with varying LA:H$_2$O ratios.

The results obtained with aqueous solutions of LA corroborated the observations for the test-reaction with an aqueous solution of acetic acid. Changing the amount of water in the system did not improve or diminish the formation of NTO, as the ketonization product. However, as can be observed in the Figure 17, the NTO peak was minimal and its presence can be considered negligible. In fact, NTO was most likely produced in reasonable quantities, but was being decomposed to other molecules such as 3-MCP (reactions in Scheme 13). The products of decomposition of NTO were clearly observed in the GC-EI-MS traces, which suggests that the decomposition is taking place as soon as NTO is produced.
Identifying the reasons why the decomposition of NTO is happening to such extent is complicated, but the observed reaction outcome suggests that the activation barrier for further reaction of NTO once formed is substantially lower than that for its formation by LA ketonization in the first place. This constitutes a formidable challenge, as the reaction is happening on the molecular level on the surface of the catalyst on really short time-scale (< $10^{-9}$ s), and we are only able to perform macroscopic alterations to improve the ketonization in despite to the side reactions.

The residence time of the substrate in the catalyst zone, was reduced from 35 min to 21 s, which resulted in improvements, especially considering that the formation of the decarboxylation product, 2-butane, was suppressed. However, 21 s is still a too long residence time, because there is enough time for NTO to decompose to side products. The differences in the WHSV values – resulting from the variation in the concentration of the aqueous solutions injected in the system – are playing an important role regarding the liquid product being observed over time. Higher WHSV values resulted in the formation of decomposition products earlier in the reactions. This was corroborated when observing the appearance of black viscous drops of liquid around 30 min into the reaction, for the experiments with WHSV higher than 0.9 g_{sub}.h^{-1}/g_{cat}. Finally, the role played by the catalyst was not clear. We are unable to define if the active sites on the CeO$_2$ also

**Scheme 13.** Decomposition reactions for NTO.
favor the aldol condensation of NTO and the hydrogenolysis of the molecule to produce 3-MCP or if the support is responsible for the side reactions. As a result, reactions applying ZrO$_2$ instead of CeO$_2$/Al$_2$O$_3$ were performed and the results are discussed in the next section.

5.5.1.3. Ketonization of aqueous solutions of levulinic acid applying ZrO$_2$ as a catalyst

The reactions with ZrO$_2$ resulted in the same product distribution as the one observed for reactions with CeO$_2$/Al$_2$O$_3$. The production of NTO was not considerably improved; however, some conclusions can be drawn from the data obtained.

Both CeO$_2$ and ZrO$_2$ are reported in literature as exceptional ketonization catalysts and, although this activity was not observed for the ketonization of LA, they provided similar results. Considering this aspect, the challenges in obtaining NTO from the LA are likely associated with the self-reactivity of this molecule, i.e. intrinsic to the substrate. As previously discussed, the presence of additional functionality in the LA molecule compromises the stability of the substrate. This results in the ketone obtained from the reaction interacting with the solid surface of a catalyst at high temperatures and suffering decomposition.

The reduction of the residence time of the substrate in the catalyst zone did not promoted a considerable variation in the products obtained thus far, but its reduction diminished the formation of highly decomposed products (an absence of the black viscous liquid). This experimental parameter can still be altered individually or in combination with WHSV variations and better results could be achieved (these reactions will be explored in the next sections). In addition to changing the interaction between substrate and catalyst, based on the results obtained with acetic acid, the solvent can also be replaced. Considering that H$_2$O is a by-product in almost all the reactions taking place with LA and its products, the replacement of water by an organic solvent
could promote better selectivity towards the formation of NTO and stop additional side reactions from taking place.

5.5.1.4. Ketonization of levulinic acid dissolved in different organic solvents

The rationale behind the selection of toluene and acetone to perform reactions with LA is both related to the solubility of the substrate, but also the fact that these solvents most likely would not suffer any transformations or decompositions at high temperatures. However, what was not expected was that the substrate and the products would react with the solvent molecules generating undesired products.

Using toluene as a solvent not only promoted side reactions between solvent, substrate and products, but also affected how the flow system behaved. The large variations in flow and the constant interruption in the production of liquid provided results that were similar to the ones observed in the reaction of methanol with acetic acid. These observations – combined with factors such as NTO not being observed, the complex mixture of products, and the toxicity of toluene – discouraged the application of this solvent in further ketonization reactions.

At first, acetone appeared to be the ideal solvent to perform the ketonization of LA. This molecule is a ketonization product, that will not further react under ketonization conditions, it has a relatively low toxicity, and it can be obtained from biomass. However, its seemingly unreactive nature during ketonizations is reserved to its production starting from acetic acid. As Figures 21 and 22 showed, the distribution of products for the reactions performed using acetone as a solvent was as complex as the ones observed by Schlaf et al.\textsuperscript{30} in their reactions with RM. At all the temperatures and flow conditions applied, the presence of acetone caused immediate formation of side products that could
not have their structure fully determined. These results also discouraged the use of acetone in further reactions in the shorter reactor with reduced catalyst load.

5.5.1.5. **Ketonization of aqueous solutions of levulinic acid applying a shorter reactor (2.5” reactor)**

The increase in the Ar flow, reduced the residence time of the substrate in the catalyst bed, as expected. However, such changes did not strongly impact the products obtained in the ketonization of the aqueous solutions of LA. The physical changes observed in the liquid products and the recovered catalyst, were mainly useful to determine which Ar flow should be selected to perform the next series of reactions (variation in feed flow rate).

Similar results were observed when the feed flow rate was altered. In this case, the decrease in the feed flow results in a decrease of the WHSV values observed. This decrease generally represents less substrate in contact with the catalyst over time, which could be translated to less decomposition of both substrate and products; however, in the case of the ketonizations performed with LA, the variations of WHSV did not directly impact the product distribution. The macroscopic variations observed in the liquid products and the recovered catalyst were only a guide to define which value was chosen to perform the next series of reactions (variation in reaction temperature).

The last series of reactions performed in this setup, evaluated the impact of the temperature in the product distribution for the ketonization reaction of LA. The reduction in the reaction temperature, could be associated with a larger amount of unreacted LA, leading to a decrease in both the formation of NTO and the other side products that have been observed. This result is in agreement...
with the literature\textsuperscript{25-28, 32, 34} and, for other carboxylic acids, ketonization of the substrate is generally achieved at temperatures above 350 °C.

As demonstrated by the data provided, the attempts to obtain and isolate NTO in appreciable yields from LA were unsatisfactory in all the reactions attempted during this project and only marginal quantities of this product were observed. The internal reactivity of LA due to the presence of the ketone, not only resulted in the formation of large amounts of $\alpha$-AL and $\beta$-AL, but also contributed to the further decomposition of NTO to products such as 3-MCP.

When analyzing the data obtained, the reactivity trends that were observed, followed the known trends for ketonization reactions, especially considering the macroscopic changes in the liquid products obtained and the catalyst recovered from the reactions. However, these trends were not observed in the GC-EI-MS traces. The macroscopic adjustments that were performed – variation of reaction temperature, catalyst, feed and carrier gas flow rate – were not able to successfully alter the interactions occurring at the molecular level between the substrate and the catalyst surface.

For example, lower reaction temperatures did result in large quantities of unreacted LA, supporting previous observations that ketonizations require high temperatures to successfully occur. The residence time was one of the experimental parameters where the variations drastically changed the products obtained. When this value was reduced from minutes (batch and RBF system) to seconds (flow reactions) the product distribution changed, and NTO was observed. However, even with residence times of 5 s, NTO rapidly decomposed to other products. The observations highlighted here, and the ones discussed in the other sections, help demonstrate the large impact that the ketone functionality of LA had on the reactivity of this molecule. This reactivity was discussed by Dumesic \textit{et al.}\textsuperscript{11} and the decomposition of LA at high temperatures was prominent.
over acidic surfaces. However, for this project the CeO$_2$/Al$_2$O$_3$ and the ZrO$_2$ were selected as catalysts due to their amphoteric characteristics.$^9,65,69$

Therefore, the conclusions that can be drawn from the data acquired are: (i) the macroscopic experimental parameters can be altered, but they do not lead to satisfactory production of NTO; (ii) the reactions taking place at the molecular level on the surface of the catalyst cannot be predicted without the application of more detailed high level computational methods; (iii) the presence of the ketone functionality in LA highly impacts the ketonization reaction, by either decomposing the substrate before the reactions can occur or by promoting further reactivity of the products obtained, both preventing the selective transformation to NTO in high yields.

Considering the high impact of the ketone functionality in the ketonization of LA, changes were performed to the substrate (production of cyclic ketals) before the substrate was injected in the flow reactor. These modifications are not ideal, for three major reasons: (i) the desire of this project was to perform ketonization of LA without requiring any alterations, which improves the atom efficiency of the reaction; (ii) the synthetic method applied in the synthesis of the LA cyclic ketals uses highly toxic solvents, which is in contrast to the principles of green chemistry; (iii) there is no guarantee that the LA cyclic ketals will survive the reaction conditions, because they can decompose at high temperatures and be deprotected through acid catalyzed hydrolysis by small amounts of acid and water present during the ketonization reaction or elimination reactions.

5.5.1.6. Ketonization applying protected levulinic acid

The decision to protect LA with EG resulted from the unsuccessful attempts of producing NTO from unaltered LA in meaningful quantities. As previously discussed, the presence of the ketone functionality in LA considerably increased its self-reactivity, which was also observed in the
ketonization products. Performing modifications to LA was not in the original scope of this project. As previously mentioned, the processes originally applied to obtain NTO relied on the application of organic reactions that could not be applied in industrial scale. The reactions performed to obtain LACEA and LACEAHE deviates from the green chemistry approach of this project. However, the inability to obtain NTO from LA prompted the testing and utilization of such an approach.

5.5.1.6.1. 
*Levulinic acid cyclic ethylene acetal (LACEA)*

The synthesis and satisfactorily characterization of LACEA were achieved and ketonization reactions were performed using this substrate. The substrate was a liquid, which allowed its injection as a pure substrate into the system, but diluting LACEA with an organic solvent was considered aiming to reduce over-exposure of the substrate to the catalyst surface. Dibutyl ether was selected as the solvent due to the fact that LACEA was miscible in it, and because this solvent is commercially available in water free form – an important characteristic considering that the deprotection of LACEA is an acid catalyzed hydrolysis \(^{58}\) and it only undergoes marginal decomposition under ketonization conditions.

As observed in the control reactions with LACEA (Appendix C, Figure C6) and the reactions with CeO\(_2\)/Al\(_2\)O\(_3\) the deprotection of LACEA resulting in the formation of LA was inevitable. This deprotection was most likely a result of the combination of the high temperatures in which the ketonizations were performed and the hydrolysis or elimination of the ketal functionality assisted by the presence of the carboxylic acid in the molecule. Although the pure sample of LACEA, and the solution in dibutyl ether did not initially contain any water, the formation of water as a by-product in the ketonization of LACEA inside of the reactor promoted the deprotection of substrate and possibly its products. NTO was not observed as an isolated product in the GC-EI-MS traces, but 3-MCP was again observed, which suggests that the ketonization product was formed, but
readily decomposed. In addition, for the first time in flow reactions performed in this project, the reactor, and the liquid products presented substantial quantities of humin products (as a viscous high-density black liquid).

Dilution of LACEA in dibutyl ether did not overcome the formation of products originated from the uncontrollable polymerization of both substrate, product, and side-product molecules present in the system. Even at a short residence time, 10 s, the self-reactivity of the substrate and product was not overcome.

Although negative, these results are not surprising. As the pertinent literature pointed out, LA ketals are fragile and subject to deprotection at high temperatures. The results obtained are also in agreement with the data provided by Lilga et al., which demonstrated that the carboxylic acid in LACEA was strong enough to promote the hydrolysis of the ketal. In our case, marginal amounts of water – side-product of the ketonization reaction – were enough to promote the opening of the ketal.

This observation stimulated the realization of a final reaction, applying LACEAHE. This intermediate in the preparation of LACEA, has an ester functionality instead of the carboxylic acid. The rationale for this attempt is the fact that the ester cannot promote the hydrolysis of the ketal. However, the substrate was still required to survive the high reaction temperatures, which should be possible, especially considering that during the control reaction with LACEA, the substrate was still present. In addition, there is no guarantee that the ester will undergo ketonization, because the carboxylic acid, as pointed out by the mechanistic studies, is the acetal functionality that participates in the ketonization. However, we hypothesized that the ester functionality could act as a temporary, labile protection group of the acid, thus modifying the
overall self-reactivity of the substrate, while still being capable of generating the free acid by elimination of acetaldehyde (Scheme 14).

![Scheme 14](image)

**Scheme 14.** Hypothesized pathway for elimination of the labile ester from LACEAHE.

5.5.1.6.2. *Levulinic acid cyclic ethylene acetal hydroxyethyl ester (LACEAHE)*

The reactions with LACEAHE also generated unsatisfactory results in terms of NTO production. The substrate was deprotected during the reactions as a result of the temperature at which the reaction was performed. This result was expected considering the low thermal stability of LA ketals.59 This resulted in the production of LA, which further reacts to produce α-AL, β-AL and 3-MCP. In addition, no evidence that the ester portion of LACEAHE reacted in a ketonization fashion9 – which involves the interaction between the carboxylic acid with the catalyst surface producing CO₂, H₂O and the desired ketone – was found, which suggests that esters themselves cannot undergo ketonization reactions.
6. Conclusions

This project was designed to perform the ketonization of LA yielding NTO as the desired product. This reaction was not previously reported, and this was also novel when considering the application of substrates with more than one functionality. LA was selected due to its potential that has been demonstrated in the preparation of many substrates such as GVL, DALA, and 2-MTHF, among others. In addition to the potential demonstrated by LA, the product of its ketonization, NTO, has a great potential when considering the polymers industry. The hydrogenation of NTO results in the formation of the 2,5,8-nonanetriol, a 3D polymeric crosslinker that displays great potential when considering polyester and polyurethanes formulations. The prior attempts to obtain either NTO or the 2,5,8-nonanetriol, relied on complex organic reactions or substrates that could not be used on an industrial scale. The market potential of NTO along with the fact that LA cab be obtained from waste biomass made this project extremely appealing.

Attempts towards the catalytic ketonization of LA were performed applying catalysts and reaction conditions previously applied to other ketonization substrates. The results obtained throughout this project demonstrated that the presence of the ketone functionality in LA severely limits the production of NTO. In the event of its production, NTO self-reacted resulting in its decomposition to other molecules or humins. We were not able to produce or isolate any of the reaction products. The GC-EI-MS traces clearly displayed a complex mixture of decomposition products of LA (α-AL and β-AL), NTO in marginal amounts, 3-MCP, the product of the decomposition of the NTO, and a range of products that could not be properly determined.

In addition to the negative impact caused by the self-reactivity of LA, the contact time between substrate and catalyst was also identified as one of the causes for the undesirable product
distribution. Aiming to overcome this issue, a fixed-bed flow reactor was designed and built. Reactions applying acetic acid demonstrated the capability of the system to perform ketonization reactions. However, when applying aqueous or organic solutions of LA, NTO was not obtained in appreciable yields, and the same decomposition products previously mentioned were observed in large quantities.

A variety of experimental parameters were studied and altered to promote a satisfactory production of NTO. Temperature, feed flow rate, carrier gas flow rate, catalyst composition and mass were explored. Unfortunately, none of the reactions performed yielded NTO in appreciable amounts. The macroscopic variations attempted by varying the experimental parameters at which the ketonizations were performed, were not able to affect the interactions happening at the molecular level between the substrate molecules in the gas phase and the solid surface of the catalyst.

Taking into consideration that the reactions were being negatively impacted due to the self-reactivity of LA, which resulted from the presence of the ketone, LA cyclic ketals were prepared and subjected to ketonization reactions. The results obtained were also unsatisfactory. LACEA and LACEAHE were not able to survive the high temperatures and the acidic environment present inside of the reactor. The ketal functionality was either hydrolyzed or decomposed, which are results consistent with the literature. In addition, the liquid products obtained from these reactions are believed to contain the largest quantities of humins.

Therefore, future work needs to be performed, focusing on the molecular level interactions that are taking place between substrate and catalyst. Such studies need to identify the nature and form of the interactions happening at the catalysts surface and their time-scales relative to the technically achievable substrate/catalyst contact times. If such studies are performed, information regarding
molecular level modifications that need to be carried out can be acquired, and the ketonization of LA could finally become a reality. Nevertheless, the results and analysis accomplished by this project supplement the literature with data that, to-date, is not fully available, and will guide future research performed with LA.
7. Experimental

The alumina support (Al$_2$O$_3$ powder, neutral, Brockmann I and 3 mm pellets), metal nitrate (Ce(NO$_3$)$_3$.6H$_2$O), zirconium(IV) oxide (ZrO$_2$ powder) and levulinic acid (≥97%) were purchased from Sigma Aldrich. ZrO$_2$ (Alfa Aesar), 3.2 mm pellets, was purchased from Fisher. The solvents applied: benzene (≥99.0%), chloroform (≥99.5%), methanol (≥99.8%), acetic acid (≥99.5%), acetone (≥99.5%), toluene (≥99.5%) and dioxane (≥99.0%), as well as EG (≥99.5%) were purchased from Sigma Aldrich. The specific modifications performed on the support and with the nitrates are specified below.

7.1. Catalyst preparation

The procedure used for preparing the catalyst for the batch reactions was previously described.\textsuperscript{25} The first step involved the activation of the support: Al$_2$O$_3$ powder (~150 g) was mixed with HPLC grade H$_2$O (200.00 mL) until a gel was obtained. The resulting gel was transferred to crucibles and dried at 60 and 120 °C for 24 h at each one of the temperatures. This activated alumina was used in the preparation of the CeO$_2$/Al$_2$O$_3$ 20wt% catalyst using the incipient wetness technique. In this preparation, Ce(NO$_3$)$_3$.6H$_2$O (~15 g) was dissolved in HPLC grade H$_2$O (20.00 mL) and placed in a burette, activated alumina (~24 g) was placed in a beaker. The cerium nitrate solution was slowly added to the activated alumina that was vigorously agitated to ensure a uniform impregnation. After complete impregnation, the catalyst was dried at 120 °C for 12 h and calcinated in a stream of air at 450 °C for 3 h. The final product was a pale-yellow powder.\textsuperscript{25}

The procedure applied for preparing the catalyst for the flow reactions also followed the procedure previously described in the pertinent literature\textsuperscript{25}. The main differences were the use of 3 mm pellets
instead of using Al₂O₃ in the powder form, the mass of catalyst prepared and the fact that because
the pellets were used, no gel was observed and instead the pellets had a wet appearance to them.

7.2. Catalytic activity measurements

7.2.1. Batch reactor

For the reactions carried out in the batch reactor the following procedures were applied:

(i) Levulinic acid (~10 g) was added to the batch reactor and mixed with either
CeO₂/Al₂O₃ 20wt% (~1 g), commercial ZrO₂ (~1 g) or RM (~1 g) using a glass coated
stir bar that was maintained inside of the reactor during the reaction to ensure agitation.
The reactor was sealed, and the temperature was set to the desired value. After
achieving the final temperature, the reactor was maintained at this temperature for 1 h.
Experiments were carried out at 200, 250, 300, 350 and 400 ºC, for RM the experiment
was only carried out at 200 ºC, the temperature at which the Schlaf group performed
the reactions with H₂. The time necessary to achieve the final temperature varied from
40 min for the lowest temperature to 120 min for the highest temperature, resulting in
total contact time varying from 100 to 200 min.

(ii) Experiments were also carried out adding H₂O (HPLC grade) to the reactor in order to
achieve a 1:1 weight ratio of LA:H₂O. In this case, levulinic acid (~5 g) was mixed
with H₂O (~5 g) and added to the batch reactor containing either CeO₂/Al₂O₃ 20wt%
(~1 g) or ZrO (~1 g). The procedure for these reactions was the same as previously
described.
7.2.2. **RBF system**

For the reactions carried out in the RBF system, two procedures were applied in terms of the introduction of the substrate to the system, with the procedure following the appropriate literature. However, the system was the same (Figure 28).

![Apparatus used for the RBF reactions.](image)

**Figure 28.** Apparatus used for the RBF reactions.
The main parts of the RBF system are numbered in Figure 28. 1 is the point in the condenser which can: (i) be closed when the LA is added at the beginning of the reaction to the catalyst in the RBF (which is numbered as 2); or (ii) it can be used for the drop-wise addition of LA to the system. 3 is the exit of the water for the cooling condenser and 4 is the point where water is introduced. 5 is the receiving RBF, where the condensed products are collected. Finally, 6 is the exhausting port to avoid any pressure build up.

The experimental procedure for the RBF system reactions is described below:

(i) For this experiment, LA (~ 10 g) was added to a RBF containing ZrO$_2$ (~ 1 g) and a quartz coated magnetic stir bar. The RBF was placed in a beaker with sand. Applying a heating plate combined with a heating band around the outside of the beaker, the system was heated to 350 ºC. On the exit of the RBF a small condenser was added to condense any products generated in the reaction and at the exit of the condenser, a second RBF (receiving RBF) was placed. The reaction was carried out for a total of 40 min, which considers the initial 35 min necessary to achieve the final temperature.

(ii) For this experiment, only ZrO$_2$ (~ 1 g) was added to the RBF with a quartz coated magnetic stir bar. The RBF was placed in a beaker with sand. Applying a heating plate combined with a heating band around the outside of the beaker, the system was heated to 350 ºC (achieved after 10 min). The same condenser applied in the previous reaction was placed on the exit of the condenser. As can be seen in Figure 28, the condenser has an extra exit, this opening was used to introduce dropwise the LA (~ 10 g) which was melted with the help of a heating gun. The addition of LA took approximately 20 min and the system was shut down at 25 min. The collection of the liquid products followed the same procedure as the reaction previously described.
(iii) For both experimental designs, the liquid product was analyzed using GC-EI-MS.

7.2.3. Flow reactor

A fixed-bed flow reactor was built to perform the ketonization reactions. The design of the reactor was designed following a literature review of systems previously used for ketonization reactions\textsuperscript{10, 33, 37, 46} and specific considerations about the ketonization reaction of LA. The reactor had two different setups depending if a downstream or upstream reaction was to be performed. A draft of both reactor setups including its parts can be seen in Scheme 15 and a picture of the final reactor in the downstream setup can be seen in Figure 29. For the downstream reactions, two difference lengths of reactor tubes were used, 2.5 in. and 5 in.
Scheme 15. Flow reactor designed to perform ketonization reactions.
The reactor and all of its components consist of stainless-steel 316/316L. Although the ketonization reactions will not be performed at high pressure, the reactor was designed to be able to work safely at high pressures, and small changes can be made to increase the safety of the system. The reactor consists of the following parts:

(i) An HPLC pump able to achieve flow-rates as low as 0.001 mL/min and as high as 5.000 mL/min with high precision. The HPLC pump is used to feed the substrate (e.g. LA/H₂O, acetic acid, LA ketal) to the reactor.

(ii) An Argon feed, similar to N₂, Ar is a non-reactive gas that is used as a carrier gas in the system. The system includes a pressure gauge (500 psi), to ensure that we are always working with the same amount of Ar for all reactions, and a needle valve that controls the Ar feed to the reactor. In association with a pressure reader (0.027 NL/min to 0.27 NL/min) at the end of the system, the carrier gas flow can be precisely adjusted before each run.

(iii) The substrate feed and the Ar feed are mixed at the T joint that sits in the bottom of the reactor (upstream) or the top of the reactor (downstream). The liquid feed and the gas are evaporated by a heating band wrapped around the injection point which is capable of reaching 700 ºC, if necessary. The temperature is controlled by a device connected to a thermocouple placed in the outside of the injection tube, between the reactor and the heating band. The controller has a precision of ± 1 ºC.

(iv) The reactor tube is a stainless-steel tube, this can be switched between a 2.5 or 5 in. length tube, both with an internal diameter of 8.48 mm. The reactor is a fixed-bed reactor and the catalyst bed is held in place by quartz wool, the length of the catalyst bed can be adjusted using the quartz wool.
(v) The reactor is heated using a heating band wrapped around the reactor tube. The temperature is controlled by a device connected to a thermocouple placed in the middle of the catalyst bed. The controller has a precision of ± 1 °C.

(vi) The injection point and the reactor area are insulated with the help of insulator material and an aluminum insulation jacket that stays around the reactor tube. The materials are placed around the heating band, minimizing heat loss to the environment or the reactor’s structure.

(vii) After reacting inside of the tube, the products and any unreacted substrate are cooled, in a stainless-steel tube coil, which is cooled by using ice (water or dry ice), and at the end of the coil, the liquid products are retained in a round-bottom flask and the gas products are expelled to the atmosphere.

(viii) The flow is monitored by using a flowmeter that is connected to the sealed receiving RBF.
In the flow reactor experiments, the parameters described below were applied.

(i) The catalyst bed was filled by either Al₂O₃ pellets, CeO₂/Al₂O₃ 20wt% or ZrO₂ pellets (depending on the experiment, either 2.5 or 5 g of catalyst was used).

(ii) The substrate feed was prepared using pure LA ketals or acetic acid, or LA, LA ketals or acidic acid dissolved in H₂O HPLC grade, acetone, toluene, methanol, dioxane, cyclohexane or dibutyl ether. The combination, substrate/solvent, was varied depending on the reaction that was being performed. The weight ratio substrate/solvent was also altered depending on the desired reaction to be performed, varying from 1:1,
1:2 and 2:1. The solution was pumped to the system with flow varying from 0.075 to 0.300 mL/min adjusted by the HPLC pump.

(iii) The Ar flow was also varied, with values ranging from 50 to 150 mL/min prior to the injection of the substrate, and during the mixing of the substrate. The Ar feed pressure was maintained at 30.0 psi.

(iv) The injection point temperature had values varying from 190 to 280 ºC. The reactor heating band had temperatures varying from 300 to 400 ºC.

(v) Prior to the beginning of substrate injection, the reactor was maintained for 24 h at the set temperature and Ar flow. This ensured that the entire reactor and the catalyst bed was at the proper temperature prior to the start of the reaction.

(vi) The RBF used to collect the liquid products was replaced every time that the color of the products obtained in the reactor changed or considerable changes in the gas flow were observed. Observations regarding the temperature, color of products and other aspects of the reaction were made throughout the reaction.

### 7.3. Analytical determinations of the reaction products

The reaction products were analyzed using a GC-EI-MS (Varian Saturn 2000). The column employed was a 30 m Stabilwax-da (acid deactivated polyethylene glycol) running in default EI mode at constant flow rate of 0.6 mL/min helium carrier gas. The temperature program used was 50 ºC (initial temperature; hold 3.0 min) → (heating rate 18.9 ºC/min) → 200 ºC (final temperature; hold 19 min). The injector temperature was 200 ºC with a 1:200 initial split ratio.
7.4. Preparation of the levulinic acid cyclic ketals

The procedure used to prepare the levulinic acid cyclic ketals (LACEA and LACEAHE) was obtained from literature. The steps for the syntheses of the ketals is described below. The picture of the Dean-Stark apparatus used for the first step of the synthesis can be seen in Figure 30.
Figure 30. Dean-Stark apparatus used in first step of the preparation of LA ketals.
The first step for the preparation of both LA ketalts, LACEA and LACEAHE is described below.

(i) Into a 500 mL RBF, LA (~ 25 g/0.215 mol), ethylene glycol (~50 g/0.830 mol), benzene (200.00 mL) and p-toluene sulfonic acid (0.3 g) were added and maintained under agitation.

(ii) The heating plate was set to 110 °C and the system was maintained under reflux for 5 h. On top of the condenser, Ar was being flushed to avoid the introduction of moisture. All the connections had silicon grease applied to them.

(iii) During the reaction, the water, which is a product of the protection reaction was being removed with the help of a Pasteur pipette.

(iv) After 5 h of reflux, the heat was stopped, and the RBF cooled with ice. Two scoops of K₂CO₃ were added to the cooled RBF to neutralize any unreacted LA.

(v) The liquid content of the RBF was decanted and transferred into a separatory funnel and the benzene portion was separated from the unreacted LA and EG and used in the next steps of the reaction. To the benzene fraction, Na₂SO₄ was added and the liquid was transferred to a different RBF.

(vi) The benzene was removed using vacuum assisted distillation. The distillation was carried out at 55 °C for 3 h, which was considered a complete removal of the solvent. At the end of this procedure, LACEAHE is obtained as the major product. This fraction was analyzed with GC-EI-MS. Crude yield: 32.05 g; 73%.

The information presented next refers to the steps required for the preparation of LACEA.

(i) In a 1 L RBF, approximately 12 g of KOH and 150.00 mL of H₂O (HPLC grade) are mixed and the liquid is left to cool down to room temperature.
(ii) When the solution reaches room temperature, LACEAHE is introduced to the RBF and the system is left under agitation for 30 min. Following this, the temperature is increased to 70 °C and the system is left under agitation for additional 30 min. This solution is then cooled to room temperature.

(iii) Once at room temperature, 100.00 mL of chloroform is added to the aqueous solution.

(iv) An HCl solution is prepared using approximately 18.00 mL of concentrated HCl and 180.00 mL of H2O (HPLC grade). The HCl solution and the chloroform/aqueous solution containing the potassium salt of LACEA are cooled to 3 °C in an ice bath and maintained at that temperature until all the HCl solution prepared is added to the other aqueous solution. This process needs to be performed very gently with strong agitation and slowly to avoid the deprotection of the ketal. A total of 6 h is necessary to add 175 mL of the HCl solution.

(v) After the HCl is added, the liquid is transferred to a separatory funnel and the phases are separated. The remaining HCl solution is slowly added to the aqueous phase and this phase is extracted with 10.00 mL of chloroform, 5 more times. The organic phases are combined at the end of this process.

(vi) To the chloroform fraction, 30 mL of brine is added, and another extraction is performed.

(vii) To the chloroform, Na2SO4 is added to remove any remaining water. The liquid portion of this RBF is decanted into a clean RBF and the solvent is removed with the help of a rotary evaporator apparatus.

(viii) The final product is LACEA, a slightly pink viscous liquid, that was analyzed using 1H and 13C NMR and GC-EI-MS. Crude yield: 26.66 g; 77%. The NMR spectra were
collected on a 400 MHz Bruker Avance spectrometers and calibrated to the residual solvent signals. \(^1\)H NMR: (400 MHz, CDCl\(_3\)): \(\delta = 1.35\) (s, 3H), 2.05 (t, \(J = 7.6\) Hz, 2H), 2.45 (t, \(J = 7.3\) Hz, 2H), 3.96 (m, 4H), 7.28 (benzene), 11.07 (s, 1H). \(^{13}\)C NMR: (400 MHz, CDCl\(_3\)): \(\delta = 24.01\) (CH\(_3\)), 33.70 (CH\(_2\)), 64.81 (CH\(_2\)), 109.08 (C), 128.33 (benzene), 179.78 (C).

7.5. Characterization of the CeO\(_2\)/Al\(_2\)O\(_3\) catalyst

XRD data was obtained for CeO\(_2\)/Al\(_2\)O\(_3\) before and after reactions, and for the Al\(_2\)O\(_3\) support. The XRD data was collected on a STOE two circle goniometer using Cu K\(\alpha\) radiation (\(\lambda = 1.54178\) Å) produced by an ENRAF NONIUS FR571 rotating anode X-ray generator. The pattern was measured in the interval from 5 to 100 in 2\(\theta\) using a 0.02 step size and 60 s of counting time.
8. References


64. Friedel, C., Ueber s. g. gemischte Acetone. Justus Liebigs Annalen der Chemie 1858, 108 (1), 122-125.


Appendix A: Compound data sheets and assigned spectra

Compound Name: 2-Methyl-1,3-dioxolane-2-propanoic acid (LACEA)

MW: 160.07 g/mol

Appearance:
Pale pink viscous liquid

Lit. and/or notebook # and page:

First made on date:
August 4th, 2017

Made by:
Igor Cunha

\[ ^1H \text{NMR: (400 MHz, CDCl}_3\): } \delta = 1.35 \text{ (s, 3H)}, 2.05 \text{ (t, } J = 7.6 \text{ Hz, 2H)}, 2.45 \text{ (t, } J = 7.3 \text{ Hz, 2H)}, 3.96 \text{ (m, 4H), 7.28 (benzene), 11.07 (s, 1H).} \]

\[ ^{13}C \text{-NMR: (400 MHz, CDCl}_3\): } \delta = 24.01 \text{ (CH}_3\), 33.70 \text{ (CH}_2\), 64.81 \text{ (CH}_2\), 109.08 \text{ (C), 128.33 (benzene), 179.78 (C).} \]
Current Data Parameters
NAME: IC-I-069-b-08-04-17
EXPERIMENT 1

P2 - Acquisition Parameters
Date_ 20170804
Time 14:10
INSTRUM spect
FREQBD 5 mm CFPBBO 3B
FUPROG zg30
ID 42774
SOLVENT CDCl3
NG 4
DS 0
SWH 5597.015 Hz
FIDRES 0.125906 Hz
AQ 3.9999107 sec
RG 18
DW 89.333 usec
DS 10.00 usec
TE 2.95 s
DI 2.000000000 sec
TD0 1

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NOC1 1H
P1 11.00 usec
PLPW 11.000000000 W

P2 - Processing parameters
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SP 400.1300614 MHz
QOD 81.000000000
SB 0
LB 0
GB 0
FC 1.00
13C JMOD NMR
Quaternary and CH2 up, CH3 and CH down

----- CHANNEL f1 -----
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NUC1 13C
p1 10.00 uscc
p2 20.00 uscc
PLAV 38.00000000 W

----- CHANNEL f2 -----
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NUC2 13C
CRFAC[2] waltze
FCF00 90.00 uscc
PLAV 11.00000000 W
PLAV2 0.16432001 W

F2 - Processing parameters
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SF 100.6127552 MHz
NOW 0 0 0
LS 0 1.00 Hz
GB 0 1.40
Appendix B: Mass spectrometry fragmentation patterns for ketonization reaction products

The data provided below shows the fragmentation pattern for LA, α-AL, β-AL, NTO, 3-MCP, LACEA, LACEAHE and other products.

![Fragmentation patterns for α-AL and β-AL.](image)

**Figure B1.** Reference fragmentation patterns for α-AL and β-AL.
Figure B2. Reference fragmentation patterns for LA and NTO.
Figure B3. Reference fragmentation patterns for 3-MCP and 3-(3'-oxobutyl)-cyclopent-2-enone.
Figure B4. Reference fragmentation pattern for LACEA.
Figure B5. Reference fragmentation patterns for LACEAHE and LAEK.
Appendix C: Example GC-EI-MS data

Control reaction for the ketonization of an aqueous solution of LA in the absence of catalyst at 400 °C in the fixed-bed flow reactor in the downstream setup.

Figure C1. GC-EI-MS traces for LA:H₂O solutions before and after control reaction at 400 °C without catalyst.
Comparison between the use of Al₂O₃ pellets and CeO₂/Al₂O₃ 20wt% as catalyst for the ketonization of LA in a flow reactor in an upstream setup at 400 °C.

Figure C2. GC-EI-MS traces for the products of ketonization reactions taking place in a flow reactor in the upstream setup at 400 °C applying either Al₂O₃ or CeO₂/Al₂O₃ 20wt% as catalyst.
Comparison between different reaction temperatures for the ketonization of LA using CeO$_2$/Al$_2$O$_3$ 20wt% as catalyst in a flow reactor in an upstream setup.

**Figure C3.** GC-EI-MS traces for the products of ketonization reactions taking place in a flow reactor in the upstream setup at either 300 or 400 ºC applying CeO$_2$/Al$_2$O$_3$ 20wt% as catalyst.
Comparison between different weight ratios of LA:H₂O for the ketonization of LA applying CeO₂/Al₂O₃ 20wt% as catalyst in a flow reactor in an upstream setup at 400 °C.

Figure C4. GC-EI-MS traces for the products of ketonization reactions taking place in a flow reactor in the upstream setup at 400 °C applying CeO₂/Al₂O₃ 20wt% as catalyst with varying LA:H₂O ratios.
GC-EI-MS trace for the viscous black product obtained after reaction of a 1:1 weight ratio aqueous solution of LA at 400 °C in the fixed-bed flow reactor in the downstream setup.

**Figure C5.** GC-EI-MS trace for the black oil product of ketonization reactions taking place in a flow reactor in the downstream setup at 400 °C applying CeO$_2$/Al$_2$O 20wt% as catalyst.
Comparison between the LACEA before and after a control reaction (without catalyst) at 400°C in the fixed-bed flow reactor in the downstream setup.

Figure C6. GC-EI-MS traces for the products of ketonization reactions with LACEA taking place in a flow reactor in the downstream setup at 400 °C in the absence of catalyst (control reaction).
Appendix D: Pressure and temperature evolution for the ketonization of LA in batch conditions

Evolution of temperature and pressure for the reaction performed at 400 °C using only LA in the absence of catalyst in a batch reactor.

Figure D1. Pressure and temperature evolution for the ketonization of LA at 400 °C in the absence of catalyst.
Evolution of temperature and pressure for the reaction performed at 300 °C using only LA and the catalyst CeO$_2$/Al$_2$O$_3$ 20wt% in a batch reactor.

**Figure D2.** Pressure and temperature evolution for the ketonization of LA at 300 °C with CeO$_2$/Al$_2$O$_3$ as catalyst.
Evolution of temperature and pressure for the reaction performed at 300 °C using only an aqueous solution of LA and the catalyst CeO$_2$/Al$_2$O$_3$ 20wt% in a batch reactor.

Figure D3. Pressure and temperature evolution for the ketonization of an aqueous solution of LA at 300 °C with CeO$_2$/Al$_2$O$_3$ as catalyst.
Evolution of temperature and pressure for the reaction performed at 350 ºC using only LA and the catalyst CeO$_2$/Al$_2$O$_3$ 20wt% in a batch reactor.

Figure D4. Pressure and temperature evolution for the ketonization of LA at 350 ºC with CeO$_2$/Al$_2$O$_3$ as catalyst.
Evolution of temperature and pressure for the reaction performed at 350 °C using only an aqueous solution of LA and the catalyst CeO$_2$/Al$_2$O$_3$ 20wt% in a batch reactor.

**Figure D5.** Pressure and temperature evolution for the ketonization of an aqueous solution of LA at 350 °C with CeO$_2$/Al$_2$O$_3$ as catalyst.
Evolution of temperature and pressure for the reaction performed at 200 °C using only LA and RM as catalyst in a batch reactor.

Figure D6. Pressure and temperature evolution for the ketonization of LA at 200 °C with RM as catalyst.
Evolution of temperature and pressure for the reaction performed at 400 ºC using only LA and ZrO$_2$ as catalyst in a batch reactor.

Figure D7. Pressure and temperature evolution for the ketonization of LA at 400 ºC with ZrO$_2$ as catalyst.
Appendix E: DFT calculation energies

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Thermally Corrected Energy at 673 K [Hartrees]</th>
<th>Thermally Corrected Energy at 673 K [kcal/mol]</th>
<th>Thermally Corrected Energy at 673 K [kJ/mol]</th>
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<td>2 x LA → NTO + H2O + CO2</td>
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<td>3-(3'-oxobutyl)-cyclopent-2-enone + H2 → 3_methyl_cyclopent_2_one + acetone</td>
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