



CHALMERS

Synthesis of Lactide with varied bases by design of experiments, via azeotropic distillation and examine potential use of molecular sieves.

A Bachelor's Thesis within Chemical Engineering

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Abstract

An emerging issue for the nature of earth is the use of fossil fuel-based plastic ending up non-recycled all over the world. The field biodegradable plastics can be a small solution to a major problem. The compound polylactic-acid originated from renewable resources and the raw material lactic acid, is a pioneer for biodegradable plastics. It is mainly produced by two different processes, direct polycondensation, and ring-opening polymerization. The latter route is the most used commercial, and the process has several steps regularly including metal catalysts, with one being the intermediate cyclic dimer of lactic acid, lactide. For PLA to be applied in medical utilization, the process requires to be metal-free. In this study, the biomedical suitable synthesis of lactide with various parameters and methods is examined.

The method of initial focus was the synthesis of lactide together with molecular sieves as a desiccant. The aim was to be able to do the synthesis that only required one reaction vessel and test metal-free catalysts to the production of PLA suitable for biomedical applications. Formation of lactide showed by NMR, potential results as of Qualitative analysis for the most bases tested. With an increase of lactic acid in the synthesis, the start material together with the molecular sieves clogged onto another. As a result of that, neither qualitative nor quantitatively measurements were possible to be fully completed, but intentions of parameters tested showed capability.

The parameters that indicate significance was tested in the proven method of azeotropic distillation to synthesis lactide in a Dean-Stark apparatus. The following parameters were, moles ratio lactic acid to amount of base and reaction time, together with five various bases a Design of Experiment was performed. Results from the experiment demonstrated a low amount of yield, and the significant quantitatively parameters varied for the different bases. The NHCs 2-methylimidazole was the highest performing in terms of yield. A mechanism for the lactide synthesis from lactic acid is suggested in this study.

All the lactide synthesis was performed in the high environmental impact solvent toluene. Some solvents were proposed theoretically to be a sustainable substitute for toluene. 2,2,5,5-Tetramethyloxolane (TMO), was possibly the best theoretical substitute solvent, but with inaccessible of TMO, unsuccessful attempts of replacing toluene with 2-MeTHF was accomplished.

Keywords: PLA, Lactide, Ring-opening polymerization, alkali metals compounds, azeotropic distillation, molecular sieves.

List of Abbreviations

PLA – Polylactic acid

NMR – Nuclear magnetic resonance

DoE – Design of Experiment

ROP – Ring Opening Polymerization

CDCl₃ – Chloroform-d

2-MeTHF – 2-Methyltetrahydrofuran

TMO – 2,2,5,5-Tetramethyloxolane

NHCs – N-heterocyclic carbenes

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1. Introduction

1.1 Lactic acid to PLA

Lactic acid is a naturally occurred organic acid that has received a lot of attention as raw material for making polymer polylactic acid [1]. Lactic acid exists in two optically active configurations, the L-isomer and D-isomer. Commercial productions of lactic acid occur through chemical synthesis or bacterial fermentation, where the synthesis creates the racemic mixture and fermentation produce optically pure L- or D- lactic acid. Most of the world's lactic acid production takes place through bacterial fermentation due to the advantage of both the use of renewable carbohydrates and the choice of a pure enantiomer [2-3]. For the synthesis of PLA from lactic acid, a metal complex catalyst is often used. To be able to use the PLA in biomedical and microelectronic applications the catalyst needs to be metal-free. Therefore, much work and effort to develop more bio-compatible metal-free organic catalysts has been put in this area of research [4].

1.1.2 A Biodegradable Polymer

Bio-based polymers that are biodegradable into environmentally friendly products in a relatively short time are in tremendous need. The plastic products, mostly made from fossil fuels, are nowadays ending up in nature and causing huge environmental problems when a large amount of plastic is excluded from recycling [5]. PLA is almost completely biodegradable under composting conditions. A lot of research has been done on the degradation of PLA through a hydrolysis reaction of the ester bond [6]. Because of hydrolysis degradation there is a major interest in biodegradable polymers in the biomedical and pharmaceutical fields. When biodegradable polymers pass through metabolic routes their fragments are completely absorbed, without any adverse effect. Which are appealing for example drug delivery systems, porous scaffolds, surgical structures, and orthopaedical devices [7].

1.2 Modern industrial production of PLA

Synthesis of PLA is made from lactic acid is usually processed in two different paths [7-8]. The two paths are called; polycondensation and ring-opening polymerization, see Figure 1. For the route of ROP, the synthesis of lactide is decisive, because it controls the molecular weight of the polymer to have comparable properties to common plastics as polystyrene or polyethylene.

PLA are commonly blended with other types of compounds fillers like fiber- and nanoparticles, both biodegradable and non-biodegradable fillers [8]. The largest production of PLA, when this study is written, is produced in 150,000 tons a year by the NatureWorks which has its base in the US [8].

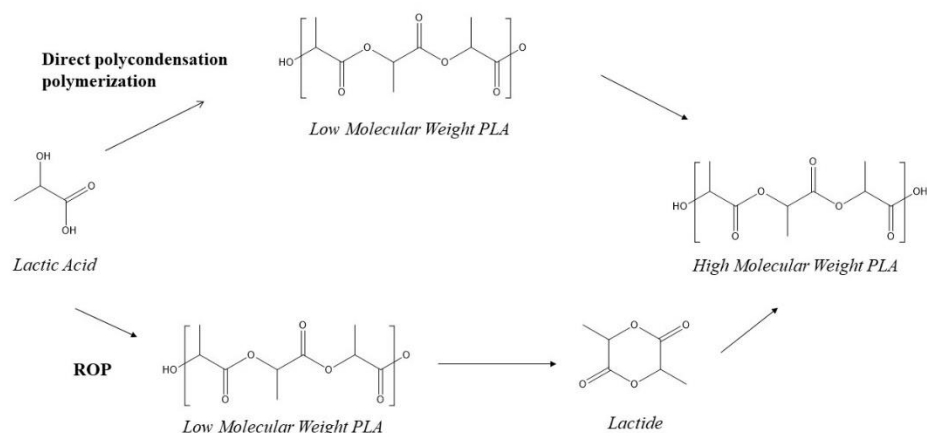


Figure 1. The two routes of polymerization of High Molecular Weight PLA [7].

1.3 Purpose and Scope

This thesis aims to examine selected parameters for the synthesis of lactide from lactic acid. The compound lactide is the crucial intermediate for the ring-opening polymerization of the biodegradable material polylactic acid. The mainly selected parameter of the synthesis is to find a catalyst suitable for use in biomedical applications, due to contemporary catalysts conflicts with toxicity for humans.

Previous research for the synthesis of lactide has been made on the proven method of azeotropic distillation. Consequently, the vision of this study is to examine a new method, with the use of molecular sieves as to trap the water in the process.

While systematic evaluation of molecular sieves, different quantitative and qualitative factors will be tested in a design of experiments format to find significant results. The ambition for choosing the chemicals for the study is to be biofriendly, leaving the product to have potential use in biomedical applications. The analyzing tools for the synthesis were limited, and NMR was chosen to be the main qualitative analytical tool for verifying the results.

2. Theory

Within this section, the features used for experiments, analysis of results, and method in this study will be introduced theoretically.

2.1 Polymerization of PLA

As introduced, there are main two courses for polymerization of PLA. The two, polycondensation and ROP, will be discussed comprehensively.

2.1.1 Synthesis with polycondensation

To synthesis a polymer with polycondensation, the monomers create a network and eliminate the waste products [10]. For the synthesis of PLA, lactic acid carbonyl and hydroxyl groups are attached, and the waste product of water is released. It may be difficult to remove the unwanted products, as with lactic acid, the water when producing PLA through polycondensation. With direct polycondensation, it forms a low molecular weight and low-quality PLA. This is why new techniques have been developed through later years, the two main paths used is azeotropic polycondensation and solid-state polymerization.

2.1.1.1 Azeotropic Polycondensation

With direct polycondensation of lactic acid, it is difficult to remove water to create a high-quality product. Azeotropic polycondensation is used to remove all water in the synthesis with a suitable azeotropic solvent [10]. To produce a high molecular weight polymer, the equilibrium can be controlled in the solvent. This also includes having chosen an organic solvent with a lower boiling point than the polymer melting point, due to risk of depolymerization and contamination.

2.1.1.2 Solid-state polymerization

Solid-state polymerization is a two-step synthesis [10]. The first step is a melting process to produce an oligomer at a temperature of 150 to 200 degrees Celsius. The second step is a state process, at a temperature between transition and melting point to increment the molecular weight.

2.1.2 Ring-Opening Polymerization

Ring-Opening Polymerization is the synthesis path most used for industrial-scale [8, 10-13]. For the ROP mechanism, firstly the lactic acid polymerizes to a low molecular weight oligomer. For the second step by the help of catalyst depolymerization to form the cyclic dimer lactide. In the last step open the ring to form high molecular weight PLA. The crucial reaction step of ring-opening polymerization is the second, that forms lactide. The formation of lactide is significant to control the properties of PLA. Catalysts are utilized to regulate the synthesis for lactide in the second step and to start the polymerization. Various catalysts that has been evaluated and tested will be discussed.

2.1.2.1 Metal-catalyst in ROP

Various metal complex is widely employed for the synthesis of lactide in ROP [4]. In the industry the use of the catalyst stannous octoate is primary, mostly due to it is granted to use for food applications. The tin (II) octoate has great properties for producing high molecular weight PLA considering its catalytic activity, high solubility in organic solvents, and easy to store. Other variations with metal complexes with oxygen groups have effective results for being able to do ROP with lactides. The factor that determines how effective a metal ion is, depends on its availability to coordinate open sites. Due to more applications for PLA for packaging and the biomedical field, development for biofriendly catalysts is required.

The mechanism for lactide polymerization with the tin (II) octoate and related metal catalysts starts with a hydroxyl group initiator to react with catalyst to set up a tin alkoxide bond. For the next step, the non-cyclic carbonyl oxygen group of lactide will briefly regulate the alkoxide bond. This leads to an increase of electrophilicity for the lactide carbonyl and nucleophilicity of the tin-oxygen group. The next stage leaves the bond between the carbonyl group and the oxygen in the cycle to be broken, which allows the lactide to open from its cycle. This interchangeable process generates and continues to polymerize as the number of lactide and catalyst is available. See Figure 2 for the later step of polymerization.

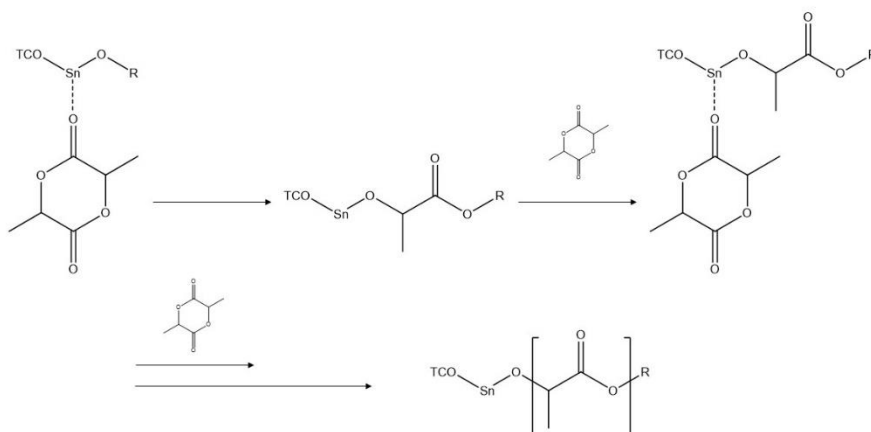


Figure 2. Mechanism for polymerization of lactide with tin (II) octoate [4].

2.1.2.2 Cationic catalyst in ROP

For cationic catalysts, ROP from lactide can be performed with strong organic acids [4]. With the use of a cationic catalyst, an alcohol initiator reacts with the carbonyl as the reaction with acid has deprotonated the carbonyl, this makes the full acid catalyst withdraw from the reaction as of its mechanism in Figure 3. The benefit of the cationic catalyst is that less catalyst is in the system and by that it is easier to remove. With acid ROP, it can by small contamination terminate the chain propagation.

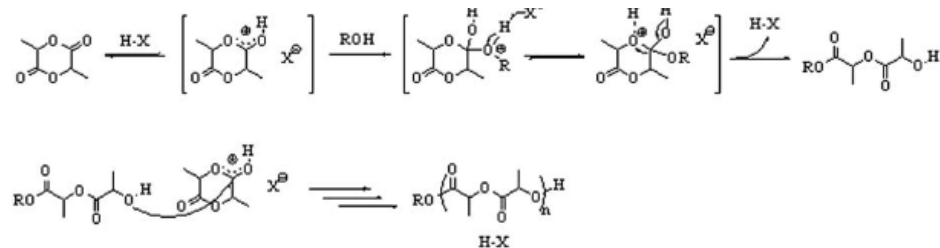


Figure 3. Mechanism for polymerization of lactide with cationic catalysts with an alcohol initiator [14].

2.1.2.3 Organic catalyst in ROP

There is a need to discover non-metal catalysts for a more bio-suitable task, as for the usage of PLA in biomedical and microelectronics utilization.

Various organic compounds can perform the ROP of lactide [14]. The first organic catalyst was the base DMAP. In Figure 4, the proposed mechanism is shown. The mechanism starts with a nucleophilic attack from the amine group of the DMAP to the carbonyl. This results in the lactide act as a zwitterionic and is permitted to initiate or propagate the hydroxyl group at the end of the chain.

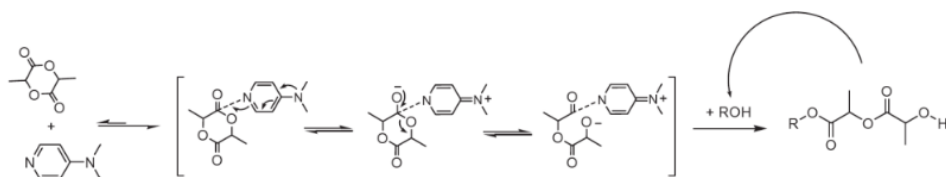


Figure 4. Mechanism for polymerization of lactide with DMAP as catalyst [14].

Another type of compound that has raised in recognition over the latest decades is the application of N – heterocyclic carbenes. It is mostly considered that NHCs influence the nucleophilic performance that benefits their organic catalyst activity, especially for cyclic esters such as lactide.

2.2 Lactide synthesis in ROP

As previously reviewed, lactide synthesis is essential for producing high molecular weight PLA in the ring-opening polymerization synthesis. See Figure 5 how lactide influence PLA.

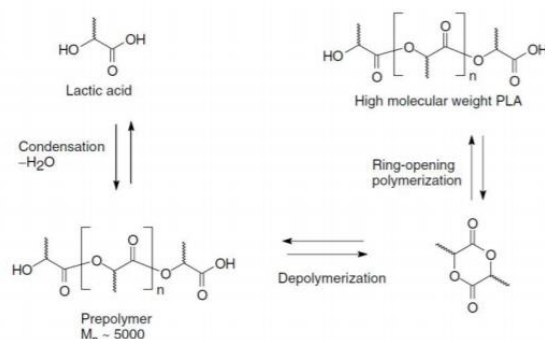


Figure 5. Demonstration for the importance of lactide in PLA polymerization in ROP [16].

Lactide is synthesized from lactic acid in aqueous conditions in two-steps [15-16]. Initially, the water is removed from the starting material lactic acid in aqueous solution to form the precursor polymer. The following phase is the esterification of the modified lactic acid prepolymer with intermolecular forces depolymerizes to lactide. In industry, both steps are operated in temperatures around 200°C . Lactide must be in pure form, if any presence of impurity, it can cause loss of molecular weight for the polymer. Crystallized lactide is not reliable to store in room temperature.

2.2.1 Lactide synthesis with coordination in basic conditions

Applying a base as homogenous catalysts to synthesis lactide has previously been experimental successful [15]. In particular, the compound cesium carbonate has accomplished to form lactide. The results from the same study a few samples with potassium carbonate, potassium hydroxide, and the NHCs 2 – methylimidazole has shown potential lactide production. A mechanism was proposed for cesium carbonate in Figure 6. In the first step of the mechanism, the pre-polymer starts propagating from lactic acid in an aqueous solution. For the second step to form lactide, it is a transesterification which is controlled by the cesium carbonate. This leads to a backbiting mechanism, which is a mechanism where the end-group reacts into the polymer chain [15].

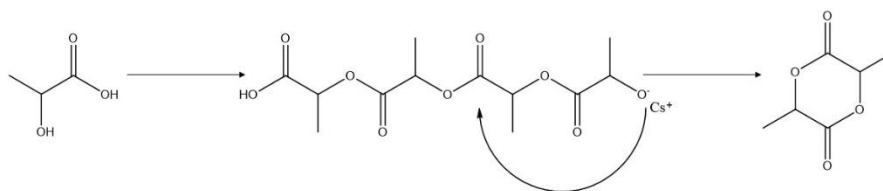


Figure 6. Mechanism of lactide synthesis with coordination of cesium carbonate [15].

2.2.1.1 Synthetic purification of lactide

For synthetic purification of lactide, it is possible to heat the lactide to its melting point at 95°C [17]. It is then added to water and stirred continuously for about 1 hour. This causes the lactide to quickly cool to the ambient temperature and creates a slurry mixture. The lactide formed crystals and filtered from the water.

2.2.2 Comparison of size with carbonate ions

As the previous section illustrated is lactide synthesis can be accomplished [15]. Carbonate ions in general defines as weak Lewis bases and the cesium ion refers to one of the largest alkali metals, see Table 1 for the size of ions [18]. Other more common alkali metals in organic synthesis and for industrial-scale are sodium- and potassium carbonates. Noticeable from Table 1 is that cesium carbonate is around 10 times the price of the more common carbonates. The prices were collected from Sigma Aldrich webpage from the 10th of May.

Hydroxyl ions compared to carbonate ions are stronger bases but relatively smaller in size [19]. Potassium hydroxide is selected in the study due it is a low-cost alternative to carbonates and has shown probable fortune for the synthesis of lactide from lactic acid.

Table 1. Comparison of alkali bases in size of ion and price per kg [18].

<i>Base/Parameter</i>	<i>K₂CO₃</i>	<i>Na₂CO₃</i>	<i>Cs₂CO₃</i>	<i>KOH</i>
<i>SEK/per kg</i>	600	644	6 220	470
<i>Size of ion (pm)</i>	138	102	167	138

2.3 Molecular Sieves

Molecular sieve is a broad term and refers mostly to fabricated zeolites made of potassium, calcium, and sodium aluminosilicates [20]. Sieves are available in different sizes for several applications. Molecular sieves from the same batch may have different behavior. The power of separation by molecular sieves can be used as absorption of water in reactions to exclude water.

2.4 The solvent Toluene

Toluene is an aromatic alkylbenzene hydrocarbon compound and it is utilized in most small scale lactide and PLA synthesis [15]. It has various commercial applications as acting as a component in petrol to be used as a solvent. Toluene has the chemical properties to be insoluble with water, but soluble in most organic solvents. It classifies as a volatile, non-polarity solvent. The health effects of toluene can be severe. If it is released in a liquid state, toluene will quickly evaporate to gas and will within a few days convert into cresol or benzaldehyde that can damage human health. Environmental effects of toluene are short-term and chronic moderate toxicity in an aquatic setting. It has low bioaccumulation and can cause damage to plants membrane [21]. Toluene is found naturally in crude oil. In EU regulation, Toluene is restricted to commercially manufacture [22]. It cannot be placed in the market with more than 0.1 weight percent for supplies to the public.

The use of toluene in the industry has over the latest decades decreased [23]. The pharmaceutical company GSK (*GlaxoSmithKline*) released a solvent selection guide in 2010, which categorizes

various solvents in environmental and health aspects. Toluene was ranked with a legislation flag that it was recommended to be substituted, due to future regulatory restrictions may be applied, predominantly for its high environmental impact [24].

2.4.1 Ecofriendly replacement for toluene

To find a suitable substitute solvent to toluene for lactide production on a laboratory scale, several candidates were analyzed. The focus was to find a solvent derived from non-fossil resources. There are several esters and ketones solvents that have been proposed as alternatives to toluene, and three potential toluene replacements were studied and surveyed in detail, 2-MeTHF, TMO, and Pinacolone.

Table 2. Comparison of toluene replacements, the azeotrope temperature, and wt.% separate is compared together with water.

Solvent/Parameter	Toluene	TMO	Pinacolone	2-MeTHF
Volatile	x	x	x	
Boiling point	110	112	106	80
Polarity	None	None	Low	Low
Azeotrope temp	85	-	-	71
Wt.% Separate	86.5%	-	-	89.4%
Solubility in water	0.52g/L	1.6g/L	19.0g/L	14.0g/L

2.4.1.1 2 – MeTHF

2 – Methyltetrahydrofuran is a solvent produced from biomass with a chemo catalytic process [25]. It is used primarily as a main replacement of tetrahydrofuran, and it is utilized in developing a chemical process, and is commercially available. 2-MeTHF is a less volatile solvent with low polarity. As seen in Table 2, it solves slightly less in water than toluene but can separate more water in an azeotropic condition.

By GSK solvent selection guide, as discussed earlier, 2 – MeTHF is ranked as a solvent with few issues. Recently it has raised in popularity for projects in pilot plants [23]. It has been questioned about its green label due to having the potential of forming explosive peroxides [24].

2.4.1.2 TMO

2,2,5,5-Tetramethyloxolane is described as the main bio-based replacement for toluene [26]. TMO, also abbreviated TMTHF, has a similar boiling point as toluene, it has the benefit of not create unsafe peroxides as ether tend to do. Related to toluene, TMO also classifies as a volatile, non-polarity solvent. The ability for TMO shows that it can produce high molecular weight polymers. It is produced from a catalytically process with a tremendously atom economy. Contemporary, there is no major industrial plant for producing TMO.

2.4.1.3 Pinacolone

The ketone-based solvent pinacolone is categorized as volatile and with low polarity [25]. Pinacolone can be produced from renewable resources. Pinacolone has a boiling point at 106°C, close to the 110°C for toluene. There is a knowledge gap for the properties of pinacolone acting as a solvent, but it has high potential replacing toluene.

2.5 Azeotrope distillation with water and toluene

A mixture of water and toluene forms a minimum boiling azeotrope [27]. The azeotrope makes it possible to sufficiently remove water from a process. The boiling point for the water and toluene mixture in atmospheric pressure is at 85°C.

2.5.1 Dean-Stark apparatus for azeotropic distillation with toluene and water

For an azeotrope distillation, a Dean-Stark apparatus is suitable [28]. Historically it is a trap to distill water out of the process. Dean-Stark apparatus is only used with solvents that have a lesser density than water. Therefore the Dean-Stark apparatus is a proper tool with the solvent toluene and water from reactants to form an azeotrope distillation. Toluene has a lesser density than water, so the water will be collected in the Dean-Stark trap [29]. A Dean-Stark trap is usually assembled with a round bottom flask connected to a Dean-Stark head, with a condenser attached to the head and heater in the bottom to boil the liquid.

2.6 Design of Experiment

The modeling term Design of Experiment is how to optimize a process with a statistical approach and used in the chemistry industry of process engineers and chemists [30]. DoE excels over the traditional “one variable at a time” testing, as it highlights how to have efficient experiments and get a holistic view of the process behavior. With low-resolution factors, usually, in a screening process, it is possible with DoE to help statistically in decisions making even though numerous of factors are dubious. From the factors, results are collected, the results are defined as responses of the input.

Usually, DoE studies is made to answer a specific science issue, and there are various types of model designs of DoE to get acknowledgment for the question. But the goal of every DoE study is to run the least amount of experiments to gather the maximum of information. The factors and responses handled in the model are classified as quantitative or qualitative.

2.7 Nuclear magnetic resonance spectroscopy

The modern spectroscopy method nuclear magnetic resonance (in short NMR) measures the absorption of electromagnetic radiation for a single nucleus placed in a constant strong magnetic field [29]. NMR permits a fast determination of chemical structure for smaller molecules, and it is well suited for synthetic work on a small scale. Studies can be made in one dimension with either proton or carbon resonance (H/C NMR), or in two dimensions where analyses can be made in correlation to protons and carbons (HSQC)

2.7.1 Quantitative NMR

To be able to quantitatively decide the concentration of products received an internal standard was mixed in the reaction [31]. With an internal standard quantitative NMR is possible, and qNMR is compared with other instrumental analytical tools an essential ratio measurement method. There are two requirements of qNMR, first, the sample needs to be fully dissolved in the solvent and it needs to have an active nucleus available for NMR.

2.7.2 References NMR spectrums

For being able to analyze the results of NMR, the analysis of published relevant research for the synthesis of lactide and PLA was scrutinized [31-36]. The following spreadsheet Table 3 is collected from previous research and predictors. All numbers are defined in solvent the CDCl₃. In Figure 7 below showcases, the atom places for each compound relative to Table 3

Table 3. The reference values for NMR spectrums, both for carbon and proton.

Atom Place	a	b	a	b	c
Type	Proton	Proton	Carbon	Carbon	Carbon
Lactic Acid	4.4	1.6			
Lactide	5.02-5.18	1.61-1.68	72.5	15.53	167.5
PLA	5.2	1.56-1.60	69.2	16.73-17.25	169.8

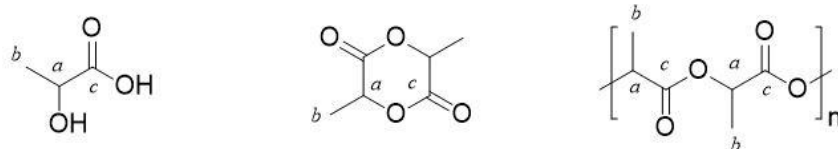


Figure 7. The atom places for respectively molecule to assist Table 3.

3. Experimental

Experiments conducted during this thesis are explained and presented in this section with a notation on how the experiment went included. The lactic acid used in this study is purchased from Sigma-Aldrich with 88-92% purity and only the isomer of L-lactic acid.

3.1 Molecular sieve as water absorber

The initial evaluation was the use of molecular sieves to remove water in the synthesis of lactide is presented in the different experimental trials.

3.1.1 Attempt with various bases in vials

The reactions were carried out in vials where 0.8g of molecular sieves were added to each vial. 5ml of the solvent toluene was added together with 0.25ml of lactic acid and the base in 0.1 moles ratio to the lactic acid. The various vials with closed lids, were placed on a hot plate at 140°C with stirring for 4 hours and then allowed to cool for 72 hours. The solvent was decanted into a round bottom flask and evaporated. The NMR sample indicates that lactide was formed for most of the samples, but the small amount of starting material and without an internal standard it was difficult to state the quantity of lactide formed. However, the method looked promising, the results are presented in Table 4. The NMR spectrums are attached in Appendix A.

Table 4. Results of attempt with various bases and their lactide indication.

Exp No	Base	Time (Hours)	Moles Ratio	Lactic acid concentration	Lactide indication
1	K ₂ CO ₃	4	1:0.1	90%	x
2	Na ₂ CO ₃	4	1:0.1	90%	x
3	CS ₂ CO ₃	4	1:0.1	90%	
4	KOH	4	1:0.1	90%	x
5	2-methylimidazole	4	1:0.1	90%	x

3.1.2 Factor trial with molecular sieves in vials

A factor trial with two bases, potassium- and sodium carbonate, were performed to investigate if any variables made a significant difference. The reactions were carried out in vials where 0.8g of molecular sieves was added to each vial. 5ml of the solvent toluene was added together with 1ml lactic acid and the base. The various vials were placed on a hot plate at 140°C with stirring for the time chosen and then allowed to cool for 72 hours. The solvent was decanted into a round bottom flask and evaporated.

Complications emerge when decanted from vials to the proper round bottom flask. A lot of the product or reactant was stuck to the bottom of the vial with the molecular sieves. Therefore, the quantitative results of the factors were hard to measure. To secure qualitative for the correct received product, an NMR test was performed for every sample. The NMR indicates that it has formed lactide in every variable tested, a selection of the sample's NMR spectra is attached in Appendix B.

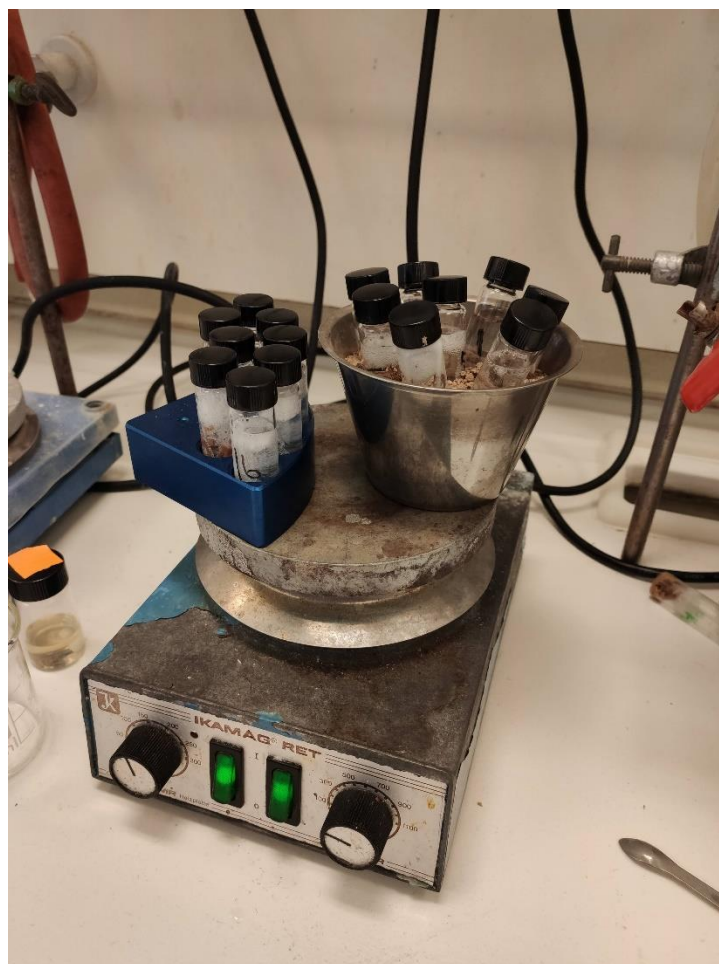


Figure 8. The set-up for the factor trial with molecular sieves.

3.1.2.1 Design of Experiment set-up in molecular sieves factor attempts

The factor trial study was designed in the software *Umetrics Modde* to create a design of experiment. The experimental order was performed in a randomized order created by the software. For the study it had three quantitative factors and one qualitative. The first factor was the mole ratio varies from 1:0.01 and 1:0.005 of lactic acid relative to the base. A second variable, the hours of reaction time, 2 and 4 hours. The third was the concentration of lactic acid, with 80% to 90%. One qualitative factor was chosen, which was what type of base that was used. The choice of variables was picked from a small screening process to find if there are any main effects and to see if there is any interaction effect between the variables. Table 5 shows the variables that were tested with the two bases, potassium carbonate, and sodium carbonate. The whole test run is attached in Appendix B.

Table 5. Presentation of the variables used for the experiment with molecular sieves.

Time (h)	Mole Ratio	Lactic acid concentration
1	1:0.05	80%
2	1:0.1	90%

Due to not fully recovered the product, the quantitative data required by the software used for modeling the experiment and plotting relevant graphs was absent. It was not possible to calculate any significant differences of the factors from the analyzed results.

3.1.3 Replace toluene with 2-MeTHF as solvent with molecular sieves

An attempt to replace toluene to a more environmental and health-friendly solvent. 2-MeTHF was chosen by the proposed solvents due to its availability. Two different bases were used in 0.1 molar ratio of the 1ml lactic acid and 5ml of solvent. The amount of molecular sieve was consistent, 0.8g in each vial. The experiment was performed with 100% 2-MeTHF and a 50/50 mixture of 2-MeTHF and toluene. The vials with closed lids were placed on a hot plate at 100°C with stirring for 4 hours and allowed to cool for 72 hours. The solvent was decanted into a round bottom flask and evaporated. Much product stuck to the bottom of the vial with the molecular sieves. This was dissolved with ethanol under heating and shown to be starting material here as well. NMR showed no indication that lactide was formed in any of the solvent combinations, see Appendix C for the results of NMR.

3.1.4 Attempt of reduced number of molecular sieves and a test with Na₂SO₄ as desiccant

The vast problem with the previous experiments was that a major amount of lactic acid was bound to the molecular sieves. To solve this problem, experiments were made with reduced number of molecular sieves to 1, 5, and 10 pieces in different vials. The desiccant Na₂SO₄ was also tested in a vial. The base Na₂CO₃ was used in a 1:0.1 mol ratio to 1ml lactic acid and 5ml toluene. The vials with closed lids were placed on a 140°C hot plate with stirring for 6 hours and allowed to cool for 24 hours. The solvent was decanted into a round bottom flask and evaporated. The NMR showed no indications that lactide had formed in any of the vials, for NMR the results see Appendix D. Also, the molecular sieves turned out to be either completely or partially dissolved in the lactic acid.

The molecular sieve method has potential but needs further study to solve the problem of lactic acid binding so hard to the molecular sieve. To be able to quantitatively analyze the lactide formed from the selected bases, the method was changed to azeotropic distillation with a Dean-Stark apparatus, which is a more proven method to synthesis lactide from lactic acid.

3.2 Azeotropic distillation with Dean-Stark apparatus

After the potential success of lactide synthesis with molecular sieves, the product was not possible to be fully isolated and collected. The experimental part will continue with the proven method of azeotropic distillation and design of experiments with some of the parameters remaining from the molecular sieve attempts.

3.2.1 Various factor attempts with azeotropic distillation

A factor test with all the five different bases was performed to investigate if any variables had a significant effect of the production of lactide. The reactions were carried out in 50ml round bottom flasks in a Dean-Stark apparatus with a capacity of 3ml. 20ml of the solvent toluene was added together with 4ml lactic acid and the base. The reaction was under constant stirring and heated in an oil bath at 140°C for the time chosen and then allowed to cool for 10 min. The solvent was

evaporated with a rotary evaporator, and an NMR sample was taken. After the evaporation, the product was in two phases, which made it hard to get trustworthy results from NMR. To find out the reliability of NMR results, one of the samples was selected to do multiple NMR samples. The results of these multiple NMR samples shown differences in the qualitative analysis and unreliability of the NMR results.



Figure 9. The set-up for the factor trial with Dean-Stark apparatus.

Due to the unreliability of NMR results, crystallization of the product was urged. The round bottom flasks with the two-phase product were heated to the melting point of lactide, at 100°C, and quickly poured into distilled water with constant stirring for one hour. With the use of ethanol, all the product was possible to be decanted to the distilled water. After one hour, the product was collected by crystallization from filtration.

The results for the product received from crystallization can be found in Appendix E. Also, in the Appendix promising NMR spectrums, reference NMR, and showcased unreliability of NMR results are presented.

3.2.1.1 Design of Experiment set-up with Dean-Stark apparatus

The DoE study was designed in the software *Umetrics Modde*. The experimental order was performed in a randomized order created by the software. The study had two quantitative factors. The first factor was a mole ratio of 1:0.05 and 1:0.025 with lactic acid to the base. A second variable, the hours of reaction time, with 1- to 2h. One qualitative factor was chosen, the selection of base. The choice of variables was picked from a small screening process with a probability to be the main effects and to see how if there is any interaction effect between the variables. To create a more reliable model of testing, three replicate runs were made with one of the bases, in 1.5 hours and a mole ratio of 1:0.0375. By adding the replicate runs, it constructs a mid-point for the experiment, and the variables can relate to the mid-point. The mid-point variables were picked by the software. The total of runs concludes to 23, as of 3 replicates mid-point samples and 20 with various variables. Table 6 shows the quantitative factors.

The following variables were tested for every base. The run order for the experiment was randomized. The selection of the bases was Cs_2CO_3 , Na_2CO_3 , K_2CO_3 , KOH , and 2-methylimidazole.

Table 6. The variables test in the experiment with azeotropic distillation.

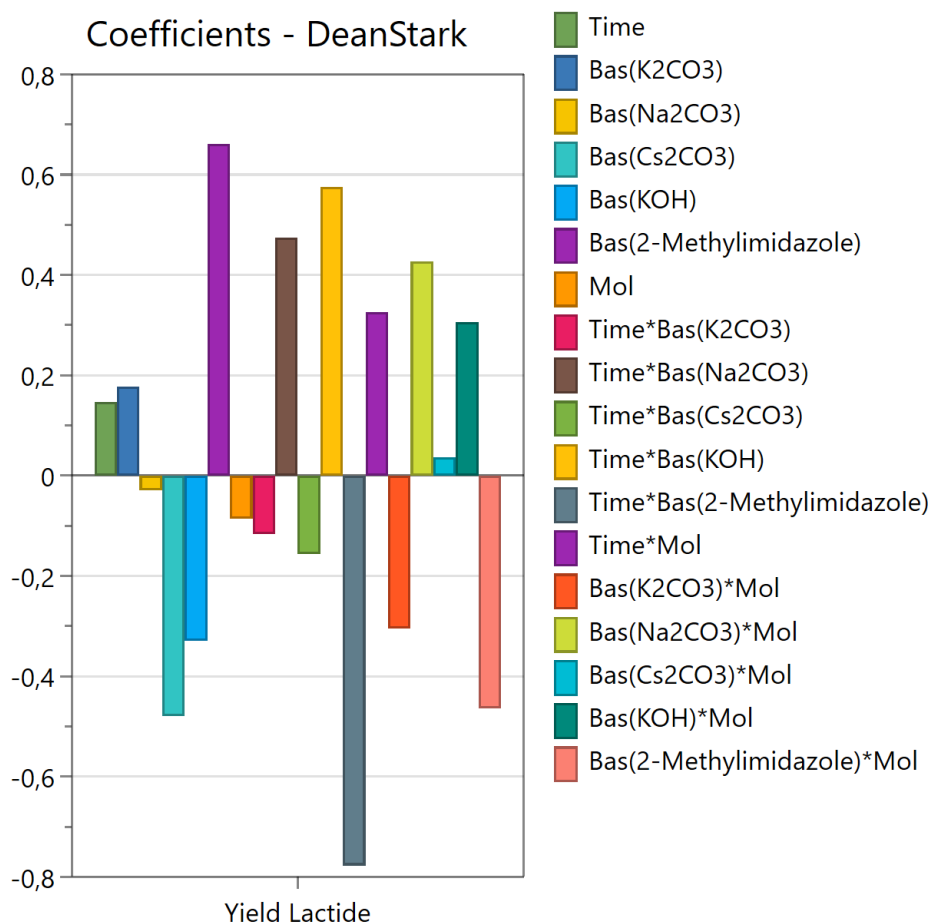
Time (h)	Mole Ratio
1	1 : 0.025
2	1 : 0.05

The quantitative response of the factors was measured in the amount of crystallized product. To secure qualitative for the correct received product, an NMR test was performed for every sample, see Appendix E for the spectrums.

The software was used for modeling the experiment and also helped with plotting relevant graphs for analyzing results. Information and help for designing the model were obtained from webinars from the software company. For this report, the use of the software and approach of DoE was a new methodology.

3.2.1.2 Results from DoE Dean-Stark

This section will go through the most important results in graphical form, from the factor trial with Dean-Stark. The graphs are collected from the software *Umetrics Modde*. Figure 10 displays the coefficients for each factor, both individual and its interplay to one another. A positive coefficient defines as an increase of yield lactide, and a negative coefficient a decrease.



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Figure 10. The bar chart shows the influences of the factors and interplays between them. The chart is generated from the software *Umetrics Modde*.

The bars in Figure 10 are color coded and are also in order from the list, top to bottom with the bars from left to right. The bars correspond to different factors, but also to the combinations of factors and what effect they have on the lactide yield. If the bars point up it have a positive effect on the yield and down, the bars have a negative effect on the lactide yield. The properties then represent the influence when this factor increases, for example, the time bar represent the effect on the lactide yield when the reactions are run over an increased time. So, where there is time*base, the bar means the influence of the lactide yield when the reaction with the chosen base is run over the longer period. From the figure, the bars with the greatest influence are the bases 2-methylimidazole and Na₂CO₃. Base Na₂CO₃ with both time and mole also have great effects, which can be seen from brown and the light green bars. From the light gray bar, 2-methylimidazole and time have a negative effect on the yield, even the number of moles has a negative effect with 2-methylimidazole. The use of Cs₂CO₃ has a similar negative effect on the yield and is shown in the light blue bar.

For both Figures 11 and 12, it visualizes four dimensions comparison. Each graph is made from a separate base. The red zones in the graphs show where the most lactide is synthesis and the opposite for the blue zone. Figure 12 shows the relation for the different carbonates in the attempt.

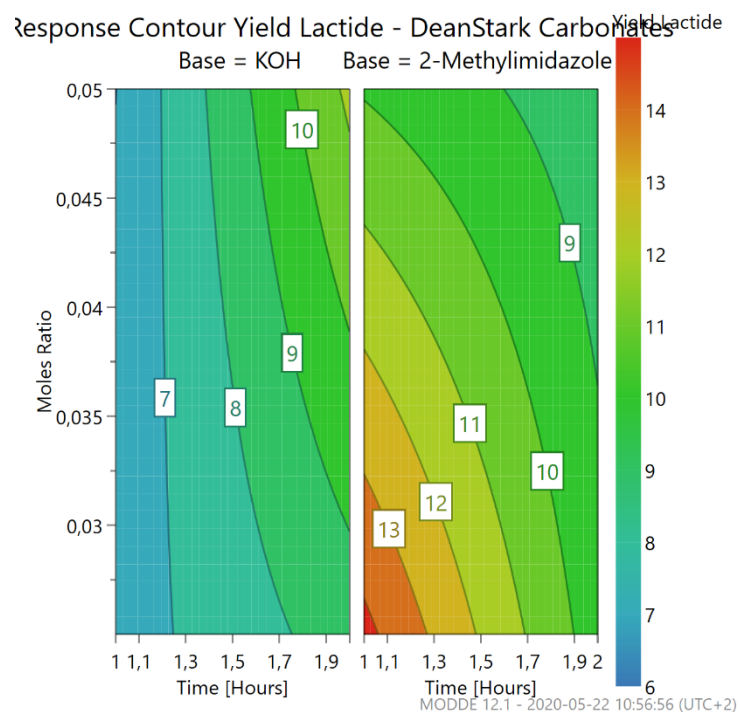


Figure 11. The 4-dimensional interplays for the bases KOH and 2-methylimidazole. The chart is generated from the software *Umetrics Modde*.

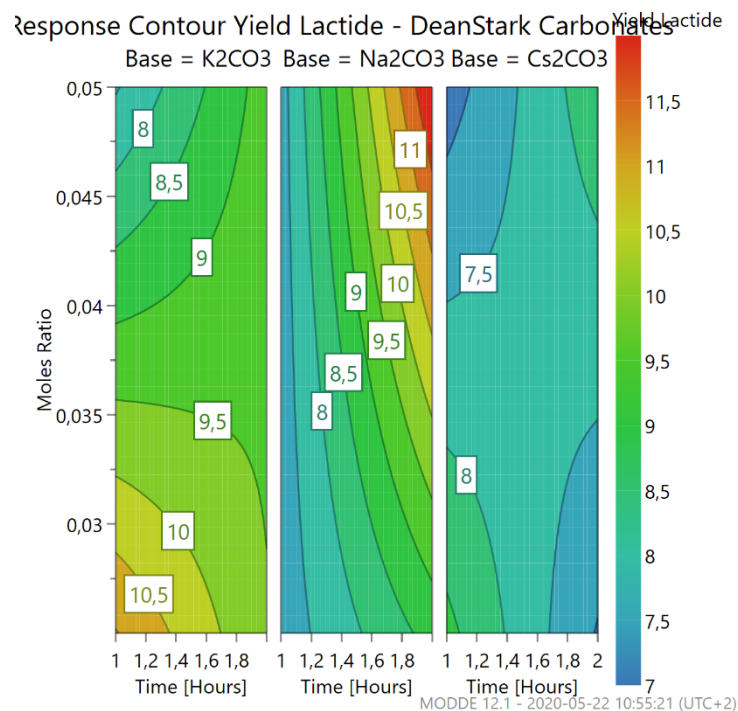


Figure 12. A comparison for the carbonate bases in the factor trial in four dimensions. The chart is generated from the software *Umetrics Modde*.

3.2.2 Replace toluene with 2-MeTHF for azeotropic distillation

Attempts to exclude that 2-MeTHF is a replacement option for toluene in the synthesis of lactide from lactic acid, 2 experiments were made. The bases Imidazole and Na₂CO₃ were used with a molar ratio of 1: 0.1 to 4ml of lactic acid and the reaction was carried out in a 50ml round-bottom flask in the 3ml capacity Dean-Stark apparatus. 20ml of 2-MeTHF was used as a solvent and the reactions were under constant stirring at 100°C for 2 hours and allowed to cool for 10 minutes. the solvent was evaporated, and an NMR sample was taken. The NMR did not indicate that lactide had been formed for any of the 2-MeTHF reactions.

3.3 Instrument used and characterization of results

For the qualitative analysis of this study, the analytical tool Nuclear Magnetic Resonance spectroscopy (NMR) was used. To determine the product received, previous research of the subject was utilized for the NMR peaks. The NMR samples were performed in the solvent CDCl₃ and spectrums of both carbon and proton NMR was analyzed. Software *MestreNova* was applied when the spectrums were studied in detail and the NMR instrument is from *Varian*. The NMR for a specific sample is attached in the appendix.

For the quantitative analysis with NMR, the compound butylated hydroxytoluene was chosen as an internal standard. Due to its high boiling point and with the potential of no interactions with

reactants. Major obstacles were obtained with analyzing results for qNMR. First and foremost, impurities in the samples made the peaks from some samples vague. Secondly the calculated integrals concerning the internal standard received figures that were unable to compare with other spectrums which make it hard to conclude.

To be able to confirm the results with NMR, references from previous research on the subject was studied. Information from Table 3 demonstrates these numbers. To get knowledge of the start material, a sample for NMR of the reactant lactic acid was tested. The sample shows an indication of polymerization, see Appendix G.

4. Discussion

In this section results from the different experiments will be discussed. It is divided into parts where the different experiments with molecular sieve and Dean-Stark are discussed separately. Then some characteristics from all experiments are discussed.

4.1 Analysis of the results from the molecular sieves experiments

An analysis of the results from the molecular sieves experiments and a discussion of the use of desiccant for the synthesis of lactide.

4.1.1 Analysis of the various bases

The results from the first experiment with the various bases indicated that lactide was formed in all reactions except in Cs_2CO_3 . To explain why Cs_2CO_3 did not give lactide, more research is needed. One explanation could be that ion interaction is created between the Cs_2CO_3 and the molecular sieves in combination with the lactic acid also binding to the molecular sieves. This maybe leads to no reaction occurring at all or that the product stuck to the molecular sieves likewise and when decanted into the round bottom flask the NMR shows neither a peak for lactide or lactic acid.

For all the other bases the results look promising and indicate that a method using molecular sieves is something to investigate further. No reflection on the lactic acid bound to the molecular sieve was made for any of the bases used at the small amount of starting material. All molecular sieves remained at the bottom of the vials, but no attention was paid to it as it is not an uncommon phenomenon that things settle when damped. Also, when the vials were rinsed, there was no problem separating the molecular sieve from the vials or each other. Therefore, it was a natural step to increase the amount of starting material to obtain a measurable yield for the factor trial.

4.1.2 Analysis of the factor trial

When the amount of lactic acid was increased to 1ml from 0.25ml, it was clear that the lactic acid bound to the molecular sieve. Thanks to the increased amount of lactic acid, this was a problem that could be detected. Unfortunately, this meant that the factor experiment did not get any significant results that could be analyzed from the quantitative variables. However, lactide has been formed in all the different experiments which are a positive indication.

One parameter was changing the lactic acid concentration which means practically varying the amount of water present. This seemed to be an interesting aspect to get an indication of how much molecular sieves needed for water present or if some combination had a significant difference. It was an active choice to examine only two bases for the factor trial. This was to keep down the number of attempts but still get an indication of the effect of the quantitative variables. The idea was to be able to change or exclude variables for a later factor trial. Then the bases could be analyzed in relation to the quantitative variables to get an indication of the influence and impact of the base.

4.1.3 Analysis of the desiccant used

A critical step in the reaction when synthesizing lactide from lactic acid is to remove the water that is created. The initial idea was to try the method where water is absorbed as the reaction takes place. To create a more efficient process by reducing the energy needed relatively for when using an azeotropic distillation to remove water. The reaction would also require a smaller amount of space as the reaction and water uptake occur in the same reaction vessel. From the first experiment with the different bases the method with molecular sieves has potential. After the problem with the increased amount of lactic acid an experiment with a minimum amount of molecular sieve was carried out. The purpose of this was to minimize the quantity of lactic acid-binding to the molecular sieve but also investigate if this small amount was enough for the reaction to work. One observation was that the molecular sieve had either completely vanished or partly dissolved due to the lactic acid. Besides, the reactions did not indicate lactide being formed. This shows that the method requires a type of molecular sieves absorbing enough water without dissolving or binding to the lactic acid or find another usable desiccant.

As of the results from the molecular sieves, a minor test with sodium sulphate as a desiccant to obtain water was pursued. The motive for the test was to try a similar resolution as for molecular sieves, to see if lactide potentially synthesized in one vial. It was difficult to separate Na_2SO_4 from the rest to be able to analyze the result. Also, in this case when the solution was decanted most of the material where left in the vial. The hope was to get an indication of lactide, like with the molecular sieve. Yet, NMR results from the minor test showed that no lactide was produced, and no optimization for the synthesis was investigated.

4.2 Analysis of the results from the Dean-Stark experiments

4.2.1 Analysis of the factor trial

From the results of the design of the experiment test with the Dean-Stark apparatus. Figure 9 presents the results of the attempts in a bar graph. The qualitative factors, the bases potassium hydroxide, and 2-methylimidazole are prominent and will be discussed in detail, and the carbonates will be studied with a comparison. For the holistic point of view of the quantitative factors. Studying the amount of yield lactide received from the attempts is to a low yield for it to be applied for industrial scale.

The results of the study show that a longer reaction time resulted in a tendency to a higher yield of lactide. Comparing the reaction times for the qualitative H-NMR spectra shows that, for a minority of the 2 hours samples, polymerization was propagated. This intends for a contradiction for the yield of lactide, and a result of the reactions going too far. Covering the mole ratio by itself, the difference of the result is marginal. So, with solely moles ratio as a parameter was inconsequential, but the interplay with moles ratio and risen time indicates a greater yield for attempts with larger parameters.

For the use of cesium carbonate alone, the production of lactide is a relatively similar level for all tries. But, the aspect of cesium carbonate is that it has the capability with interplay with reaction time and a mole ratio to lactic acid to receive a higher yield.

The NHCs 2-methylimidazole compared to sodium carbonate displays the opposite result for the factor trial. For 2-methylimidazole the lesser of reaction time and with lower moles ratio to lactic acid, greater lactide yield is received. When studying the H-NMR spectrums for a qualitative reason to this behavior, it visualizes that after 2 hours of reaction the lactide has reacted further to create high molecular weight PLA because of the various H-NMR peaks at 5.2 as of Table 3.

The three different carbonates used in the experiment, cesium, potassium, and sodium, did not have the same distinguished results as the other two bases. Figure 11 visualizes the differences between the carbonates for the quantitative factors. Sodium carbonate results indicate the tendency of increased yield as for overall time vs moles ratio in a linear trend. While for potassium carbonate contradicts and demonstrates the opposite linear regression. For cesium carbonate the quantitative variables interplay with high significance. With a rise of a single quantitative factor the yield of lactide decreases, but together the yield increases.

As of the strong base and low-priced potassium hydroxide, in terms of amount lactide crystallized is low for the less reaction time and smaller moles ratio. The benefit of KOH is its exchange of yield when raising the factor of reaction time. When inspecting the NMR spectrums that polymerization has barely begun. It may have to do with the hydroxyl ion of KOH, have the potential to react with water to the system.

4.3 Analysis of the characteristics and influences of the various bases

Shown in the result for the attempt of azeotropic distillation, the base with the most influence is 2-methylimidazole. This organic NHCs compound has similarities in structure to the DMAP described in the section of 2.1.2.3 Organic catalyst for ROP. Though the DMAP is mostly applied for synthesis from lactide to PLA, the similar 2-methylimidazole shows that it can be used for lactide synthesis of lactic acid. The amine group of 2-methylimidazole is most probably the factor to control the synthesis. When covering Figure 10, the parameters are for synthesis is crucial, with too much base and reaction time, lactide will convert to PLA as was found from the NMR spectrums.

Potassium hydroxide is as a strong base of low-cost. As discussed in section 4.2.1, the amount of yield increases with longer reaction times. Comparing its results with the other potassium ion used in the study, potassium carbonate, it contradicts each other. The size of the potassium ion is the same, but a probable cause is that the hydroxyl ion interacts with water which prolongs the process of distillation of water. Another explanation may be a measurement error caused by attempt 1 (K_2CO_3 1h 1:0.025). If the lactide crystals still contained water from the recrystallization step and therefore indicated more lactide than it was. If so, the amount of lactide formed by potassium hydroxide and potassium carbonate is quite similar in all other trials. Which would indicate that the size of the ion, not what substance it comes from, plays a part in the synthesis.

Table 7. Yield lactide from the alkali metal bases in the DoE with azeotropic distillation.

Base/Parameter	Size of ion (pm)	Lactide 1h 1:0.025	Lactide 1h 1:0.05	Lactide 2h 1:0.025	Lactide 2h 1:0.05
K₂CO₃	138	10.8%	6.5%	8.6%	9.0%
Na₂CO₃	102	8.0%	6.5%	7.9%	12.9%
Cs₂CO₃	167	8.5%	8.2%	7.1%	8.2%
KOH	138	4.3%	6.9%	10.7%	9.0%

For the three carbonates that was tested in this study, the results differentiate. The cesium ion is by its atomic radius the largest, comparing to the potassium and sodium ion atomic radius. This can be the explanation as to why Cs₂CO₃ struggles to control the backbiting from the oligomer to lactide and have less yield than the other carbonates. Sodium carbonate showed the most potential with the most yield in the right condition, the opposite explanation can be considered, as of being the smallest of the ions. This led to less steric hindrance for the ion to position itself when chain transferring to lactide. The potassium ion of the carbonates is considered as the medium size in this comparison performed beneficial in low moles ratio, which leaves fewer ions in the mix and considerably less steric hindrance for the backbiting mechanism.

4.4 Analysis of the attempt of replace toluene

There are no major differences in the properties between the solvent's toluene and 2-MeTHF when studying Table 2. This makes 2-MeTHF a highly relevant candidate to replace toluene. The solvent 2-MeTHF has a slightly lower boiling point which is a good thing from an energy perspective. There is no significant difference in wt.% water the azeotrope separates from the reaction, 2-MeTHF has a slightly lower proportion, but still high enough which indicates that the solvent is useful. In the absence of information, there are no sources for the solvents TMO and Pinacolone, if azeotrope is possible with water and what boiling point this would result in, even the amount of wt.% that the azeotrope would be able to separate. Since they are like toluene, it can be assumed that they would create a sufficiently useful azeotrope to be interesting enough to investigate further.

The attempts to replace toluene with 2-MeTHF reactions were decided to run at a lower temperature due to 2-MeTHF's lower boiling point. Something that was discovered afterward was that the reaction was now running below the boiling point of the lactic acid. This could have a bearing explanation on why no lactide was synthesized. If the reaction needs a higher temperature to reach activation. In that case the meaning of using a solvent with lower boiling point loses its purpose and further investigation of replacing 2-MeTHF with toluene was of no interest.

4.5 Proposed mechanisms for lactide synthesis in basic conditions.

From the theory of lactic acid esterification with cesium carbonate with its mechanism presented in Figure 6 and is made of a backbiting mechanism coordinated by the cesium carbonate [15]. The mechanism with the other carbonates is proposed following the cesium carbonate. As suggested previously, the matter of the size of alkali metal ion has a significantly. Figure 13 shows similarities to Figure 6 but shows the mechanism for the K_2CO_3 and Na_2CO_3 . Most likely, the mechanism for potassium hydroxide will have a similar mechanism as of K_2CO_3 .

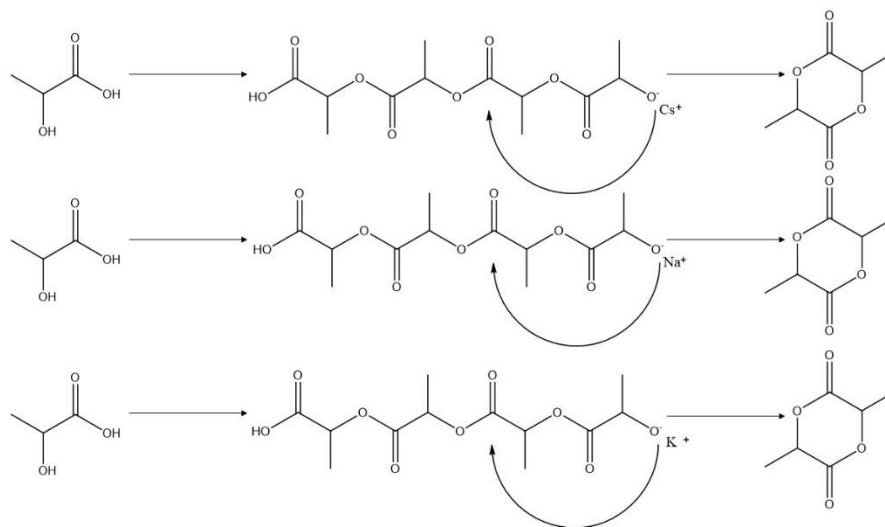


Figure 13. Proposed mechanisms for the alkali metal ions to guide in lactide synthesis.

As of the mechanism for the 2-methylimidazole theory of its mechanism is gather from the section of 2.1.2.3 Organic catalyst for ROP. The mechanism for the formation of lactide by 2-methylimidazole is possible the same as for the mechanism of formation of high molecular PLA but reverse with organic catalyst [14]. That the mechanism goes both ways and that 2-methylimidazole can coordinate to terminate the chain and create lactide of low molecular PLA and open it up to create the chain again. The mechanism is illustrated by Figure 4 with the similar molecule to the 2-methylimidazole of DMAP. This could be an explanation for why 2-methylimidazole has the best lactide yield at low moles and short times. For a long time, it reacts easily with the lactide and forms high molecules of PLA which means that the reaction has gone too far which was indicated from the experiment.

5. Conclusion

For this thesis, the main aim was to explore different possible parameters for synthesis lactide from lactic acid. The method primarily used for the synthesis was with the water-absorbing molecular sieves. With potential results from qualitative analysis with molecular sieves as a desiccant, the method was shifted to the proven method azeotropic distillation due to an inaccessible product. The molecular sieve method showed promising outcomes, and with the use of other sieve types the availability to isolate the product can be possible.

From the azeotropic distillation, the single factor with the largest influence in positive importance was the selection of base. The most major positive impact had the NHCs compound 2-methylimidazole. While the use for Cs_2CO_3 showed no significant impact on the quantitative factors. For the interplay of factors, 2-methylimidazole in a lengthy reaction time decreased the amount of yield and showed propagation of PLA. KOH , Na_2CO_3 , and K_2CO_3 showed linear results when increasing or decreasing the variables.

For the use of industrial-scale of producing lactide, potassium carbonate and 2-methylimidazole showed the most promising results with low moles ratio and short reaction time. If the process exaggerates a longer reaction time for the product, the choice of sodium carbonate or potassium hydroxide is more suitable. The amount of yield lactide received from this study is not economically defensible for production to a large extent.

With the attempts of a more environmentally friendly solvent suitable to exchange toluene, 2-MeTHF showed theoretical potential. But, shown both with molecular sieves and with azeotropic distillation, concludes that with the set-up and reaction condition practiced in this study, 2-MeTHF is not suitable for the synthesis of lactide from lactic acid.

6. Future work

For future research, lactide synthesis in basic conditions shows some potential. Especially the low-cost bases as sodium carbonate, potassium carbonate, and potassium hydroxide. Forthcoming work can be to explore the kinetics and thermodynamics for how the bases react in different conditions, and if possible, how it can increase the yield for lactide.

Optimization of the method with molecular sieves can lead to successful results. The primary focus of future research should focus on how to separate the product from the sieves. Investigation of different types of molecular sieves with other capabilities is within an interest.

To find a suitable replacement for toluene, 2-MeTHF should not be studied further with the reaction conditions used for this study. The promising solvent TMO as a green replacement of toluene. If accessible, the application of TMO in the process can be an interesting option.

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APPENDICIES

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Appendix A. Attempt of various bases with molecular sieves.

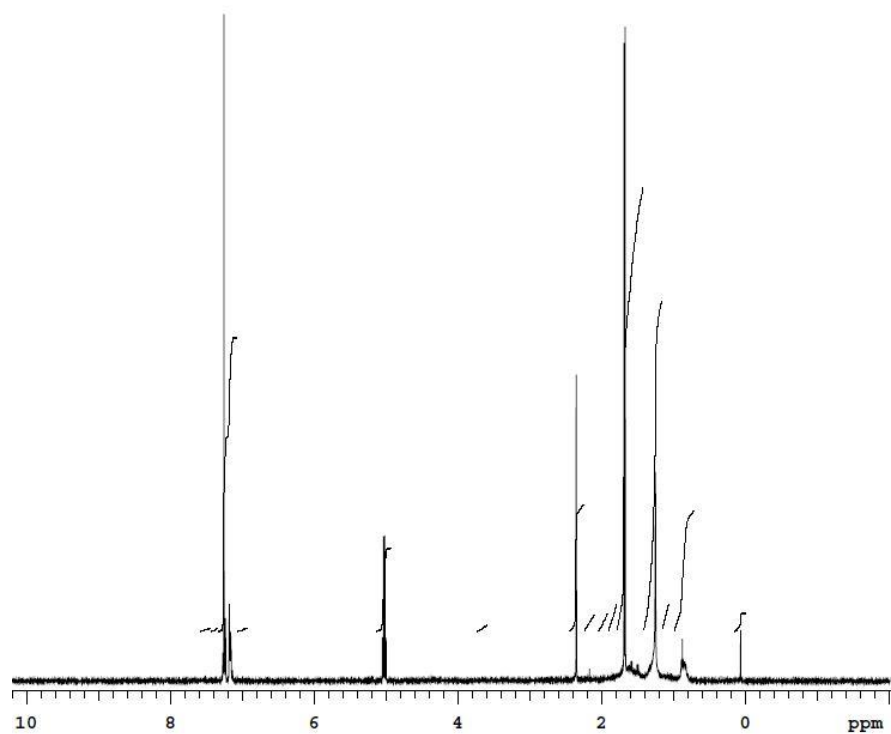


Figure A1. Proton NMR spectrum for K_2CO_3 with molecular sieves.

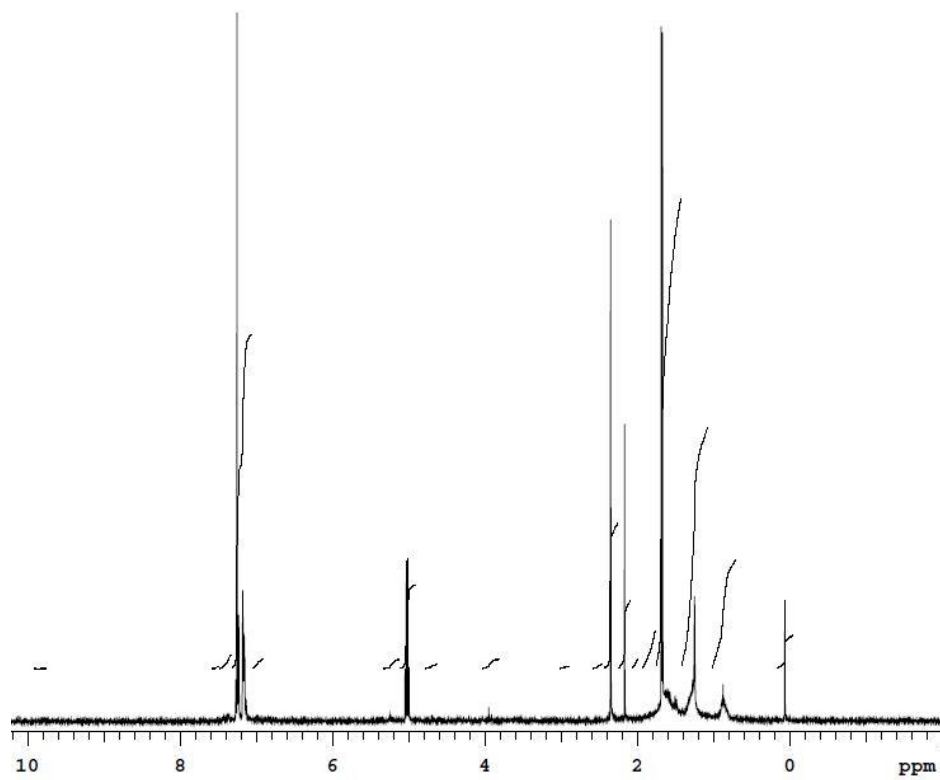


Figure A2. Proton NMR spectrum for Na_2CO_3 with molecular sieves.

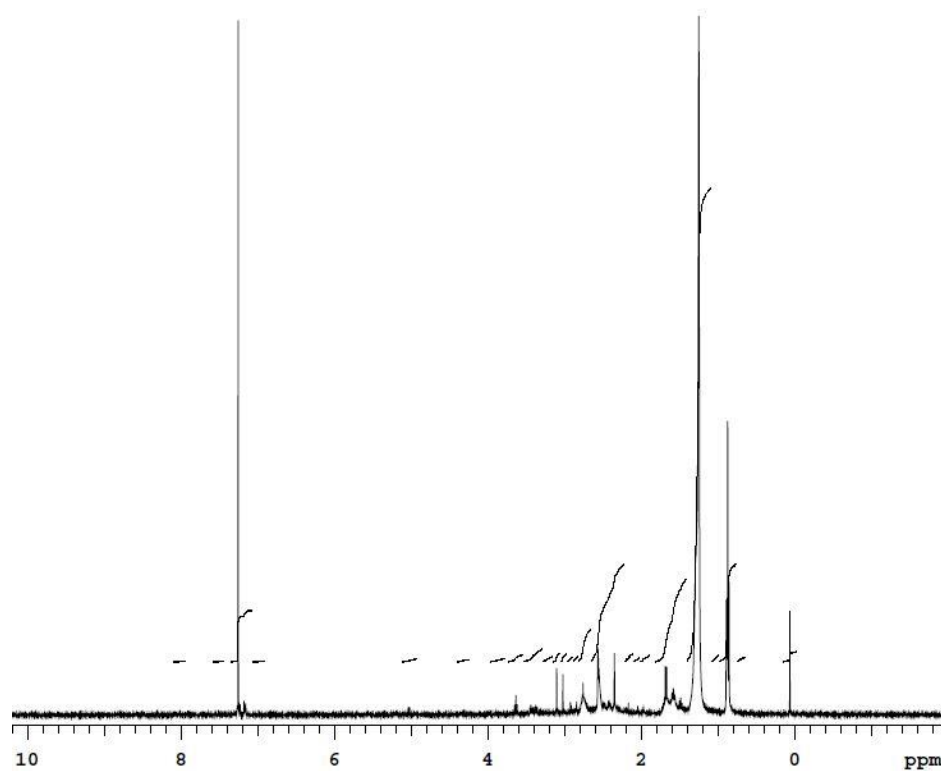


Figure A3. Proton NMR spectrum for Cs_2CO_3 with molecular sieves.

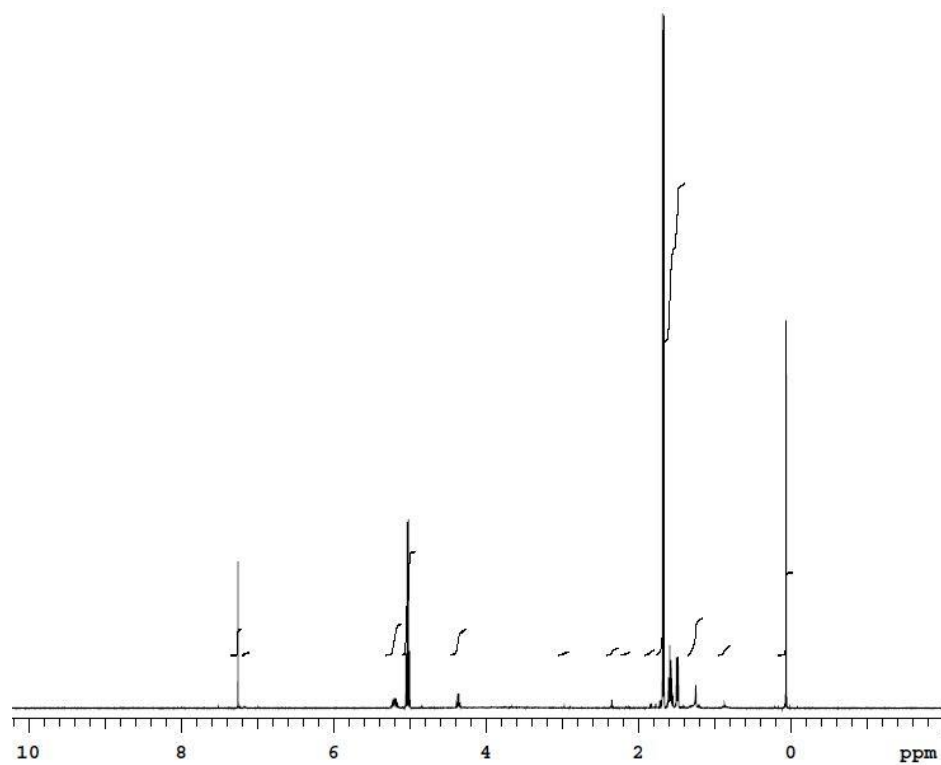


Figure A4. Proton NMR spectrum for KOH with molecular sieves.

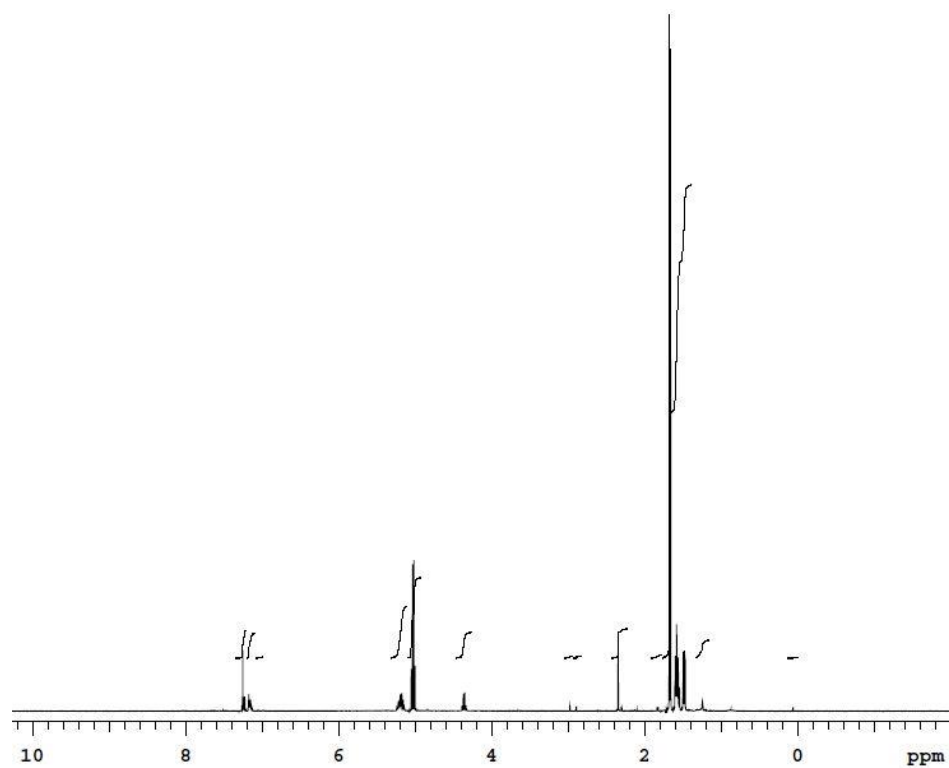


Figure A5. Proton NMR spectrum for 2-methylimidazole with molecular sieves.

Appendix B. Factor trial with molecular sieves

Table B1. The factors in the test design of experiments for molecular sieves.

Exp No	Base	Time (Hours)	Mole Ratio	Lactic acid concentration
1	K ₂ CO ₃	2	1 : 0.05	80%
2	Na ₂ CO ₃	2	1 : 0.05	80%
3	K ₂ CO ₃	2	1 : 0.05	90%
4	Na ₂ CO ₃	2	1 : 0.05	90%
5	K ₂ CO ₃	2	1 : 0.1	80%
6	Na ₂ CO ₃	2	1 : 0.1	80%
7	K ₂ CO ₃	2	1 : 0.1	90%
8	Na ₂ CO ₃	2	1 : 0.1	90%
9	K ₂ CO ₃	4	1 : 0.05	80%
10	Na ₂ CO ₃	4	1 : 0.05	80%
11	K ₂ CO ₃	4	1 : 0.05	90%
12	Na ₂ CO ₃	4	1 : 0.05	90%
13	K ₂ CO ₃	4	1 : 0.1	80%
14	Na ₂ CO ₃	4	1 : 0.1	80%
15	K ₂ CO ₃	4	1 : 0.1	90%
16	Na ₂ CO ₃	4	1 : 0.1	90%

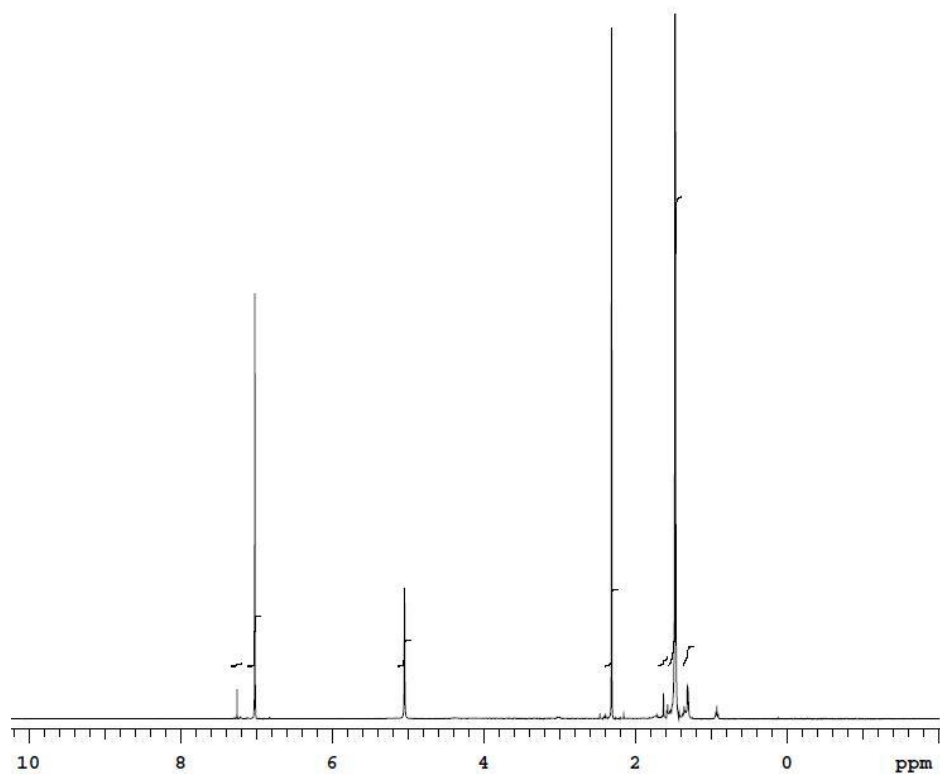


Figure B1. Proton NMR spectrum for factor attempt number 1 with molecular sieves.

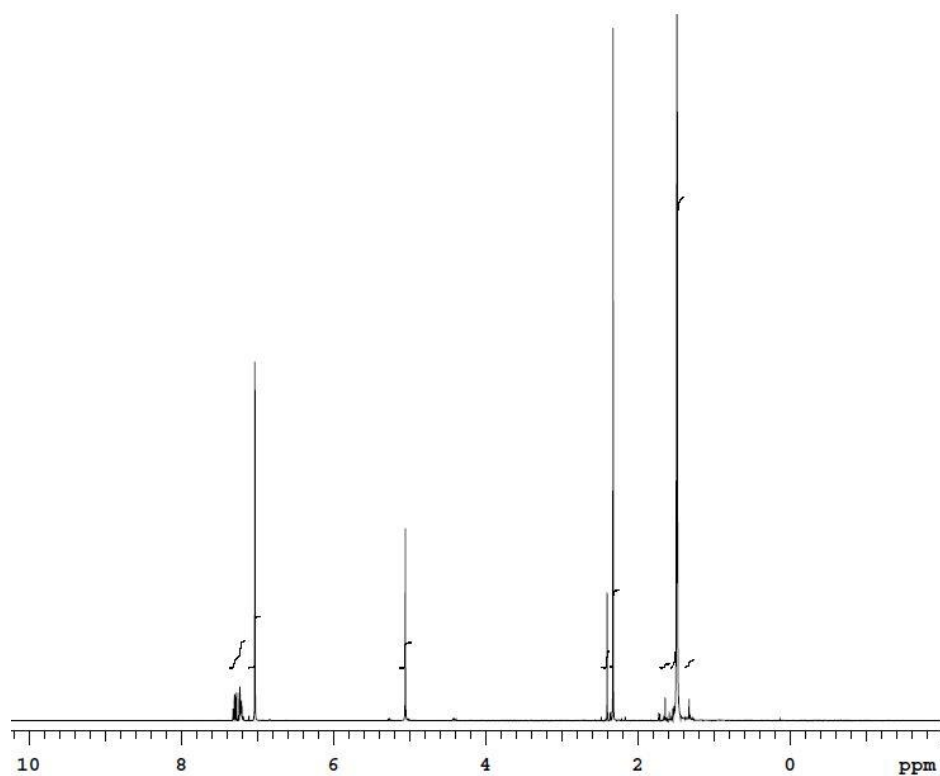


Figure B2. Proton NMR spectrum for factor attempt number 2 with molecular sieves.

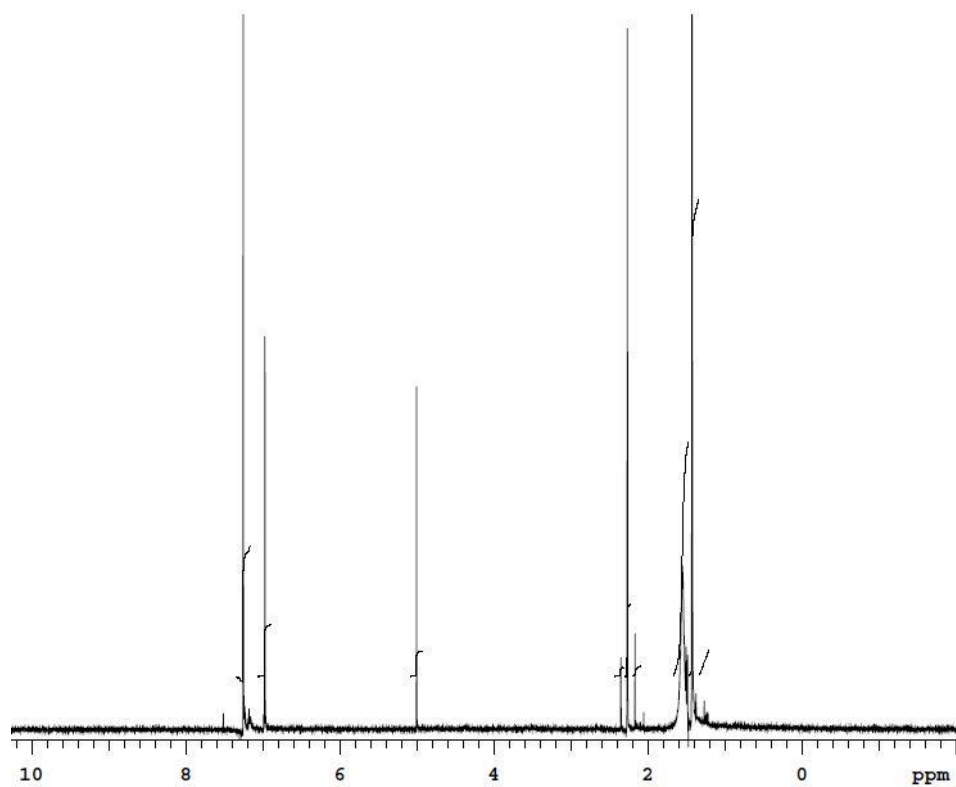


Figure B3. Proton NMR spectrum for factor attempt number 5 with molecular sieves.

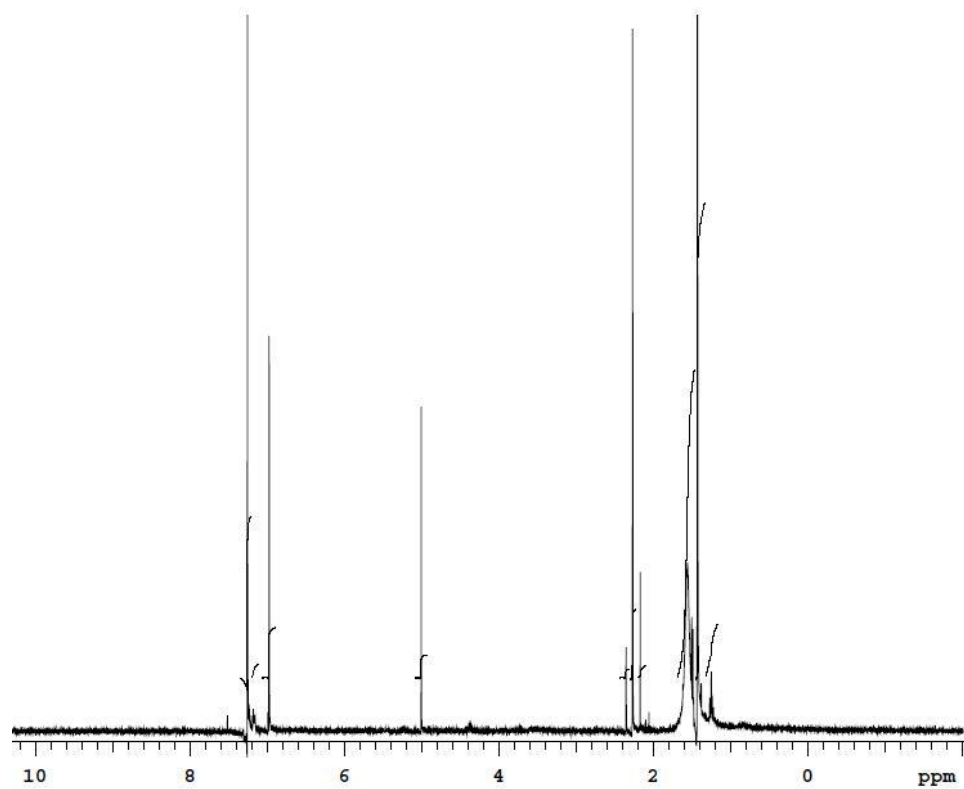


Figure B4. Proton NMR spectrum for factor attempt number 6 with molecular sieves.

Appendix C. Attempt of replacing toluene with 2-MeTHF with molecular sieves

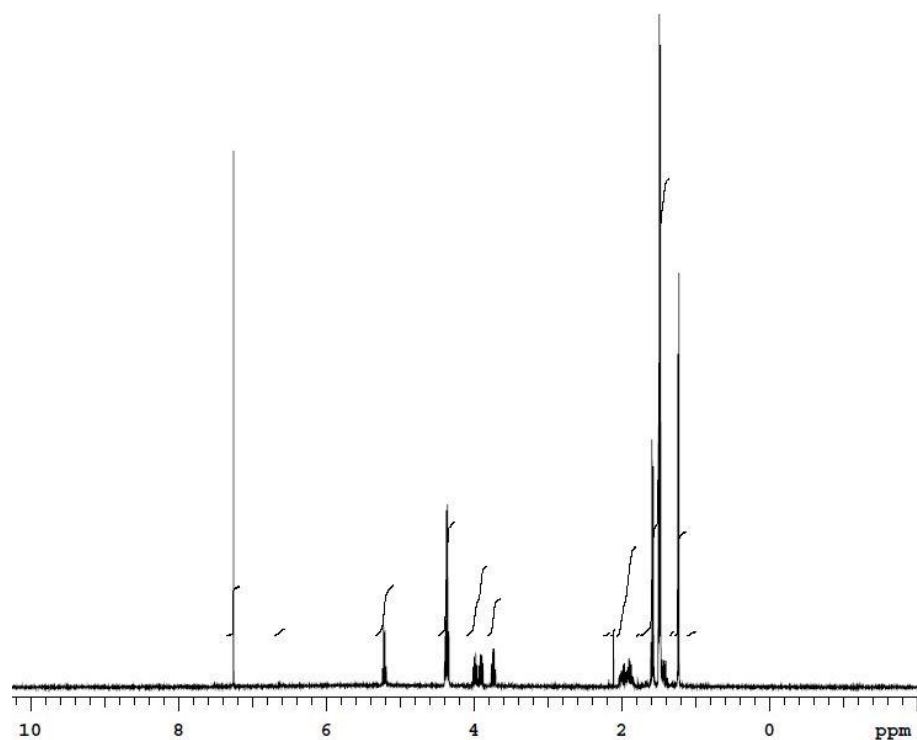


Figure C1. Proton NMR spectrum for attempt with 2-MeTHF as solvent with K₂CO₃.

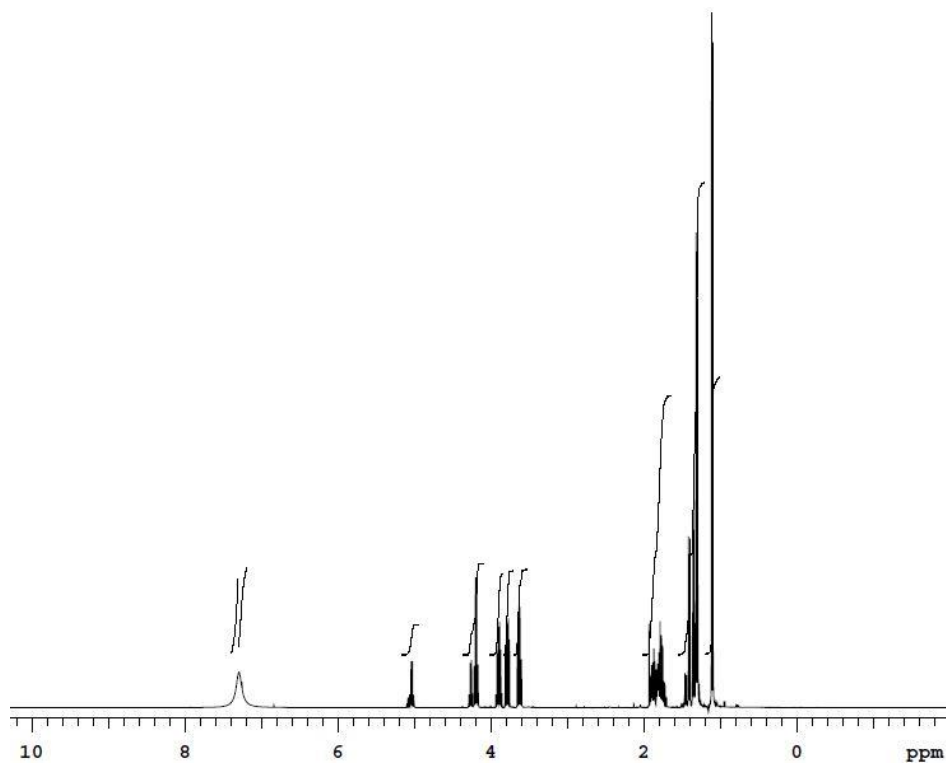


Figure C2. Proton NMR spectrum for attempt with 2-MeTHF as solvent with Na₂CO₃.

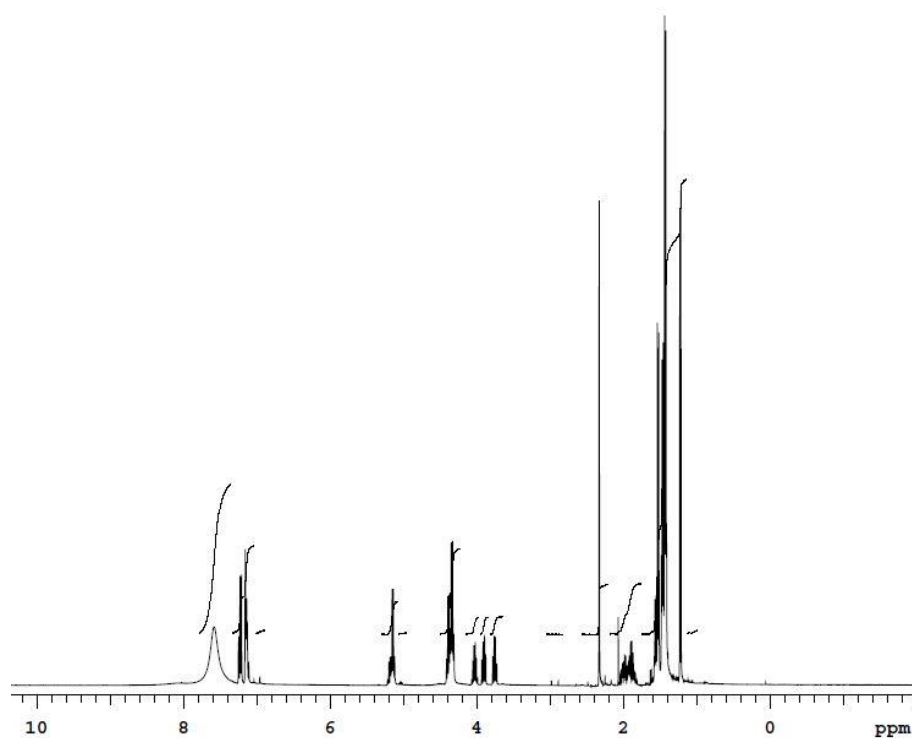


Figure C3. Proton NMR spectrum for attempt with a mix of 2-MeTHF and toluene as solvent with Na_2CO_3 .

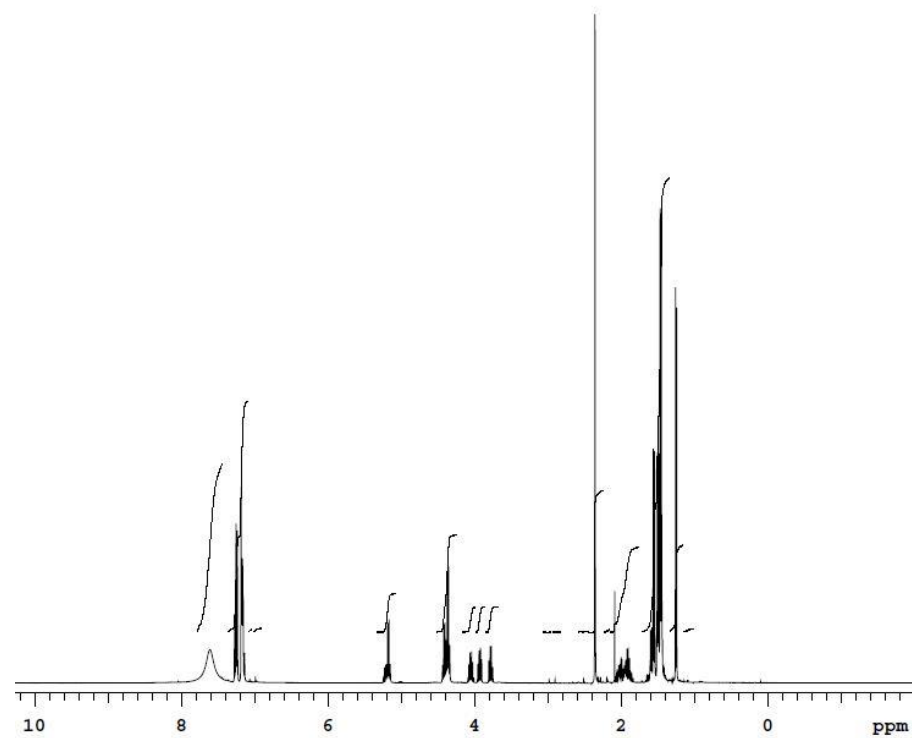


Figure C4. Proton NMR spectrum for attempt with a mix of 2-MeTHF and toluene as solvent with KOH.

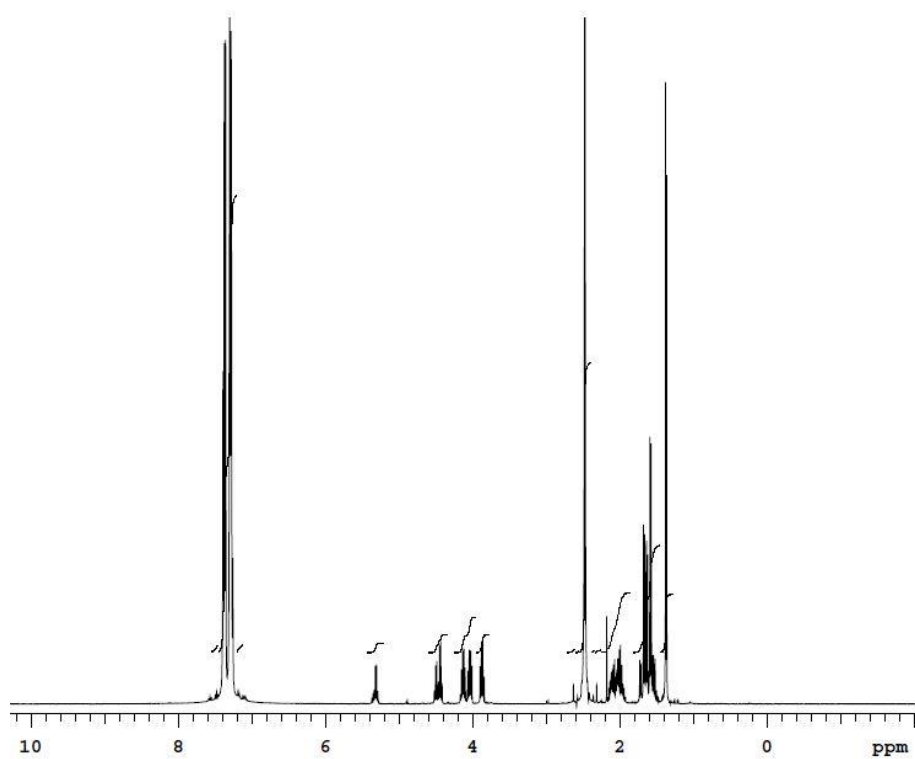


Figure C5. Proton NMR spectrum for attempt with a mix of 2-MeTHF and toluene as solvent with 2-methylimidazole.

Appendix D. Attempt with reduced amount molecular sieve and test with the desiccant Na_2SO_4 .

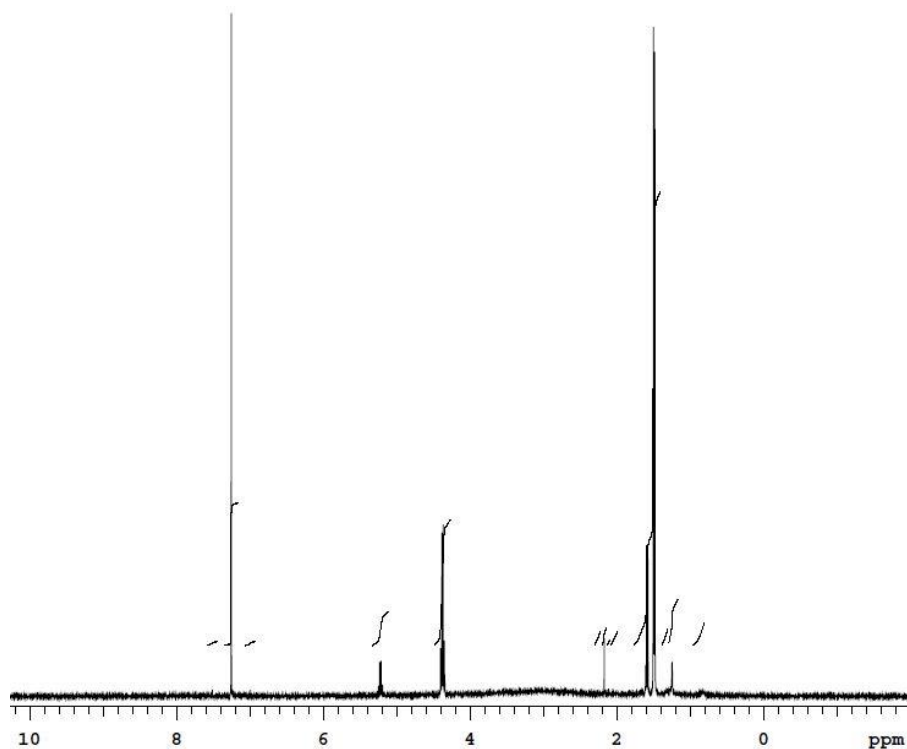


Figure D1. Proton NMR spectrum for attempt with one molecular sieve as desiccant.

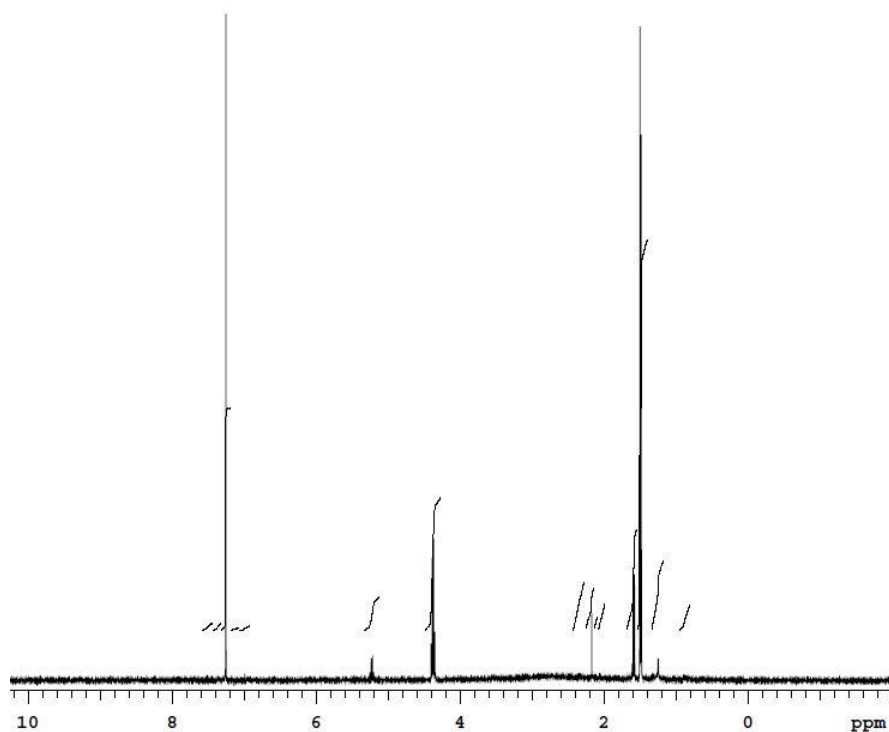


Figure D2. Proton NMR spectrum for attempt with 5 molecular sieves as desiccant.

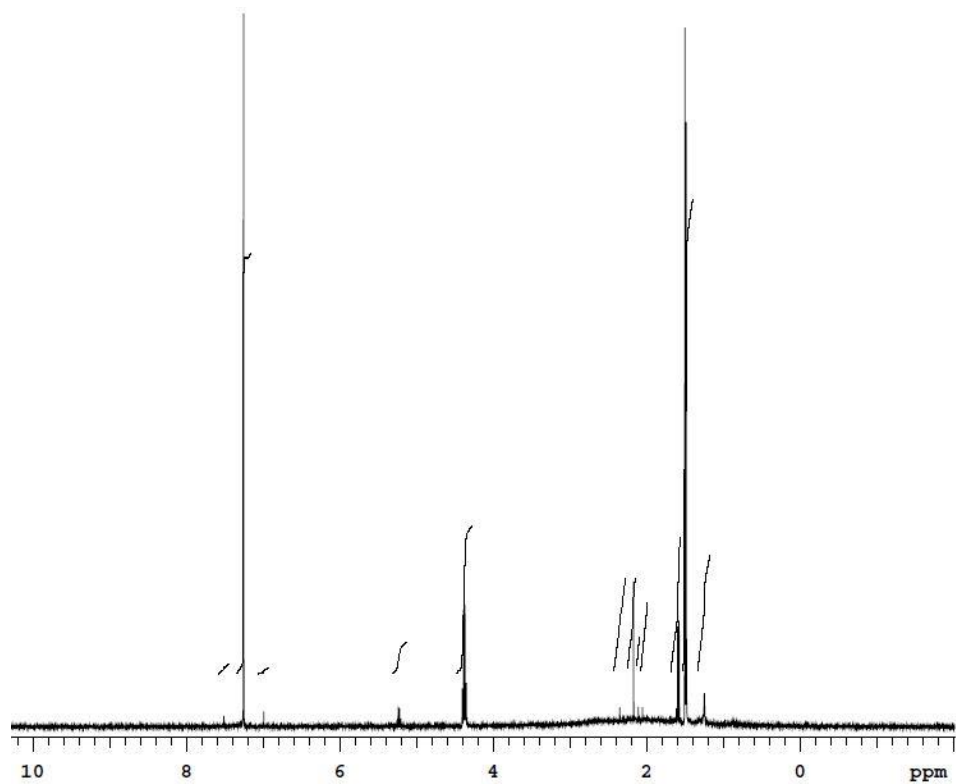


Figure D3. Proton NMR spectrum for attempt with ten molecular sieves as desiccant.

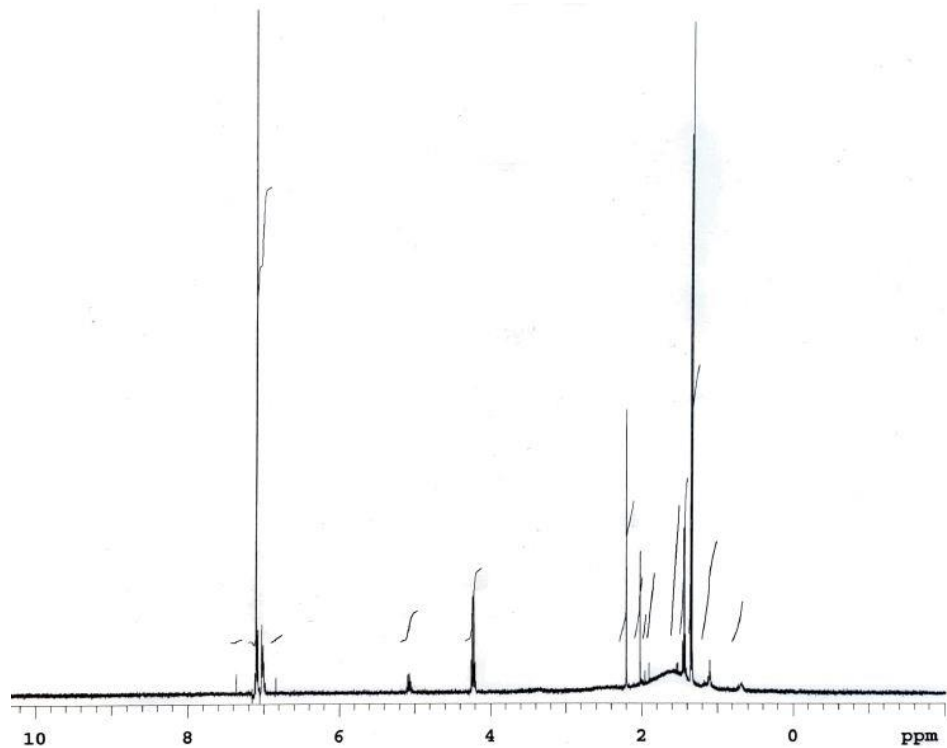


Figure D4. Proton NMR spectrum for attempt Na₂SO₄ with as desiccant.

Appendix E Factor trial with azeotropic distillation

Table E1. The factors in the test design of experiments for azeotropic distillation.

Exp No	Run Order	Base	Time (Hours)	Mole Ratio	Yield lactide (%)
1	21	K ₂ CO ₃	1	1 : 0.025	10.8
2	3	K ₂ CO ₃	2	1 : 0.025	8.6
3	23	Na ₂ CO ₃	1	1 : 0.025	8
4	8	Na ₂ CO ₃	2	1 : 0.025	7.9
5	2	KOH	1	1 : 0.025	4.3
6	9	KOH	2	1 : 0.025	10.7
7	7	Cs ₂ CO ₃	1	1 : 0.025	8.5
8	18	Cs ₂ CO ₃	2	1 : 0.025	7.1
9	13	2-methylimidazol	1	1 : 0.025	15.5
10	15	2-methylimidazol	2	1 : 0.025	8.3
11	19	K ₂ CO ₃	1	1 : 0.05	6.5
12	6	K ₂ CO ₃	2	1 : 0.05	9
13	16	Na ₂ CO ₃	1	1 : 0.05	6.5
14	4	Na ₂ CO ₃	2	1 : 0.05	12.8
15	1	KOH	1	1 : 0.05	6.9
16	14	KOH	2	1 : 0.05	9
17	22	Cs ₂ CO ₃	1	1 : 0.05	8.2
18	12	Cs ₂ CO ₃	2	1 : 0.05	8.2
19	11	2-methylimidazol	1	1 : 0.05	8.7
20	20	2-methylimidazol	2	1 : 0.05	9.6
21	10	K ₂ CO ₃	1.5	1 : 0.0375	7.3
22	17	K ₂ CO ₃	1.5	1 : 0.0375	9.1
23	5	K ₂ CO ₃	1.5	1 : 0.0375	13.9

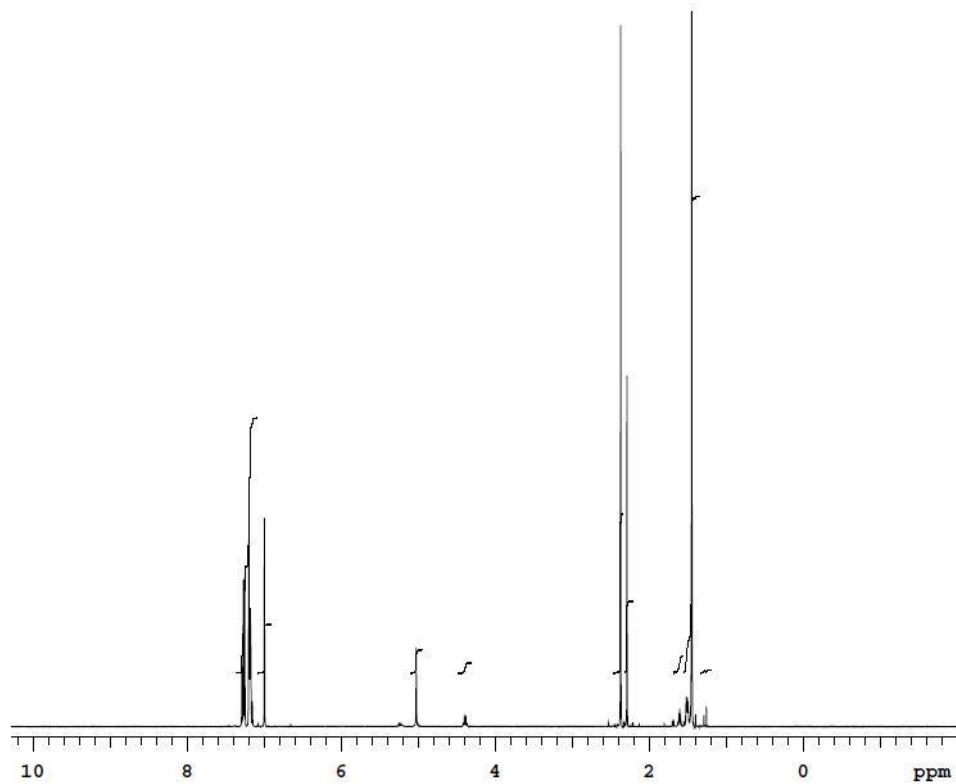


Figure E1. Proton NMR spectrum for experiment number 1 with azeotropic distillation.

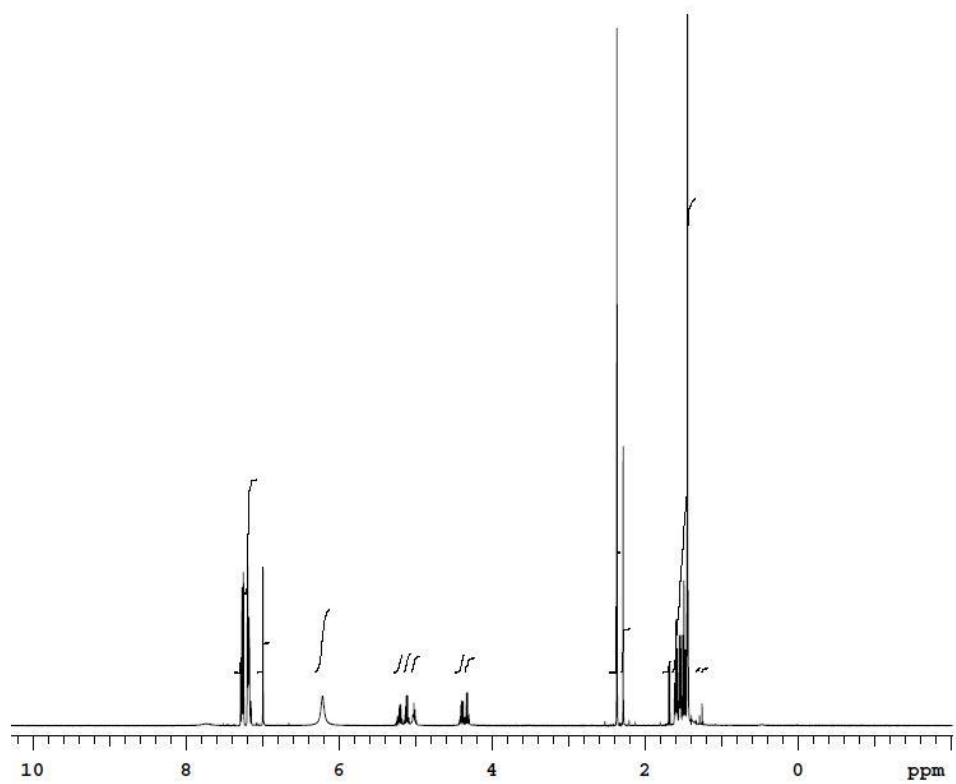


Figure E2. Proton NMR spectrum for experiment number 14 with azeotropic distillation.

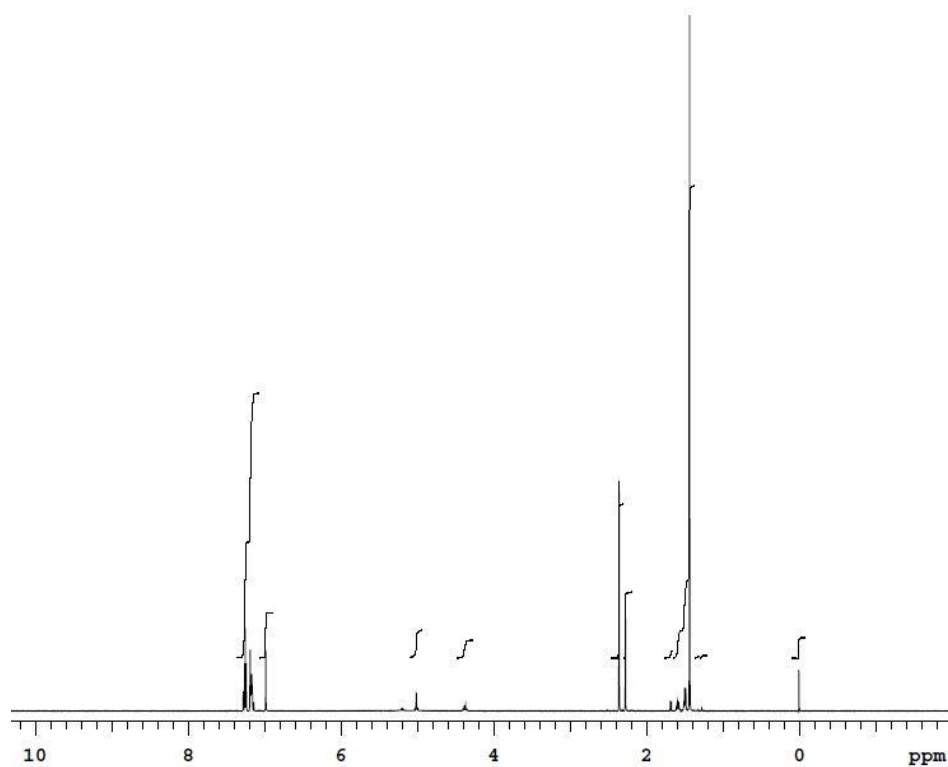


Figure E3. Proton NMR spectrum for experiment number 6 with azeotropic distillation.

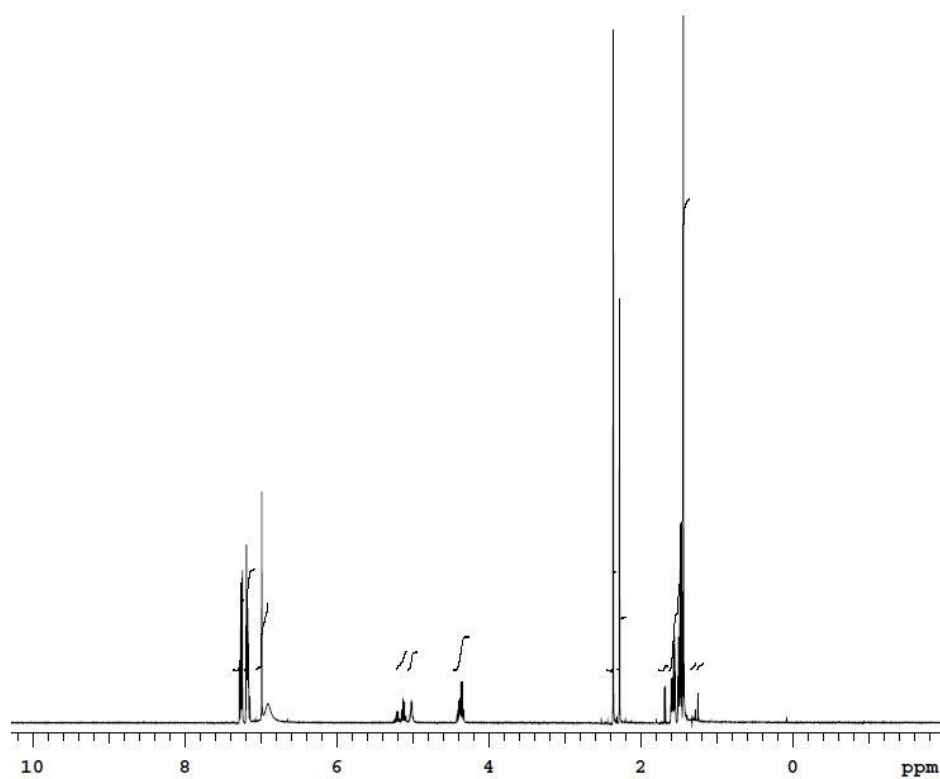


Figure E4. Proton NMR spectrum for experiment number 7 with azeotropic distillation.

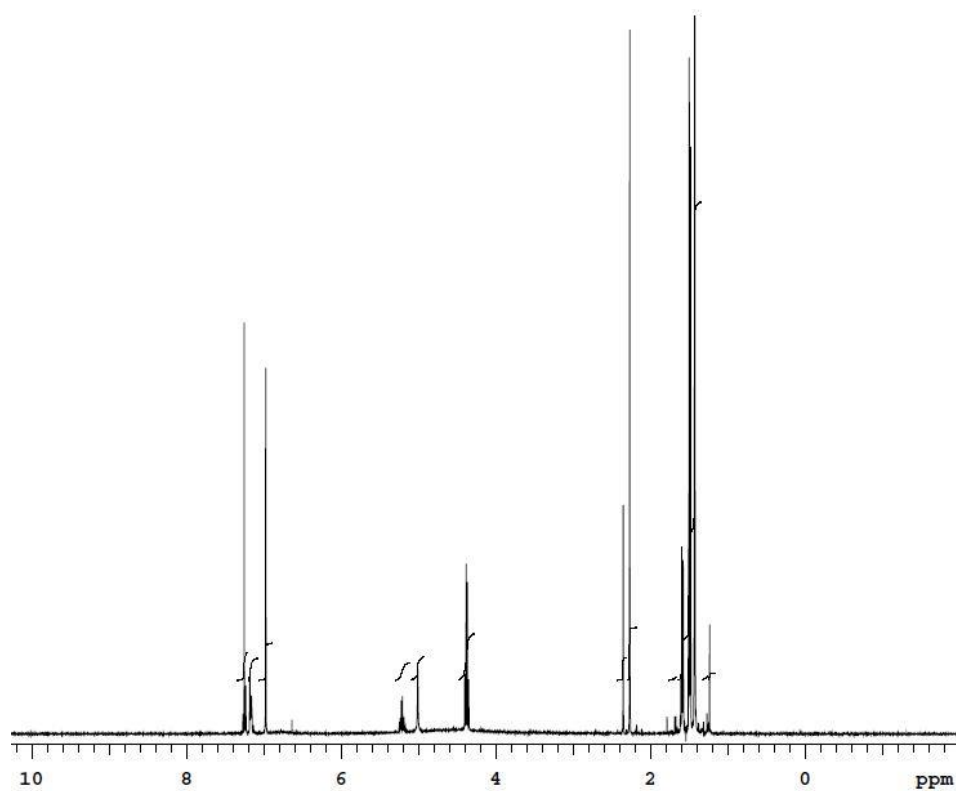


Figure E5. Proton NMR spectrum for experiment number 9 with azeotropic distillation.

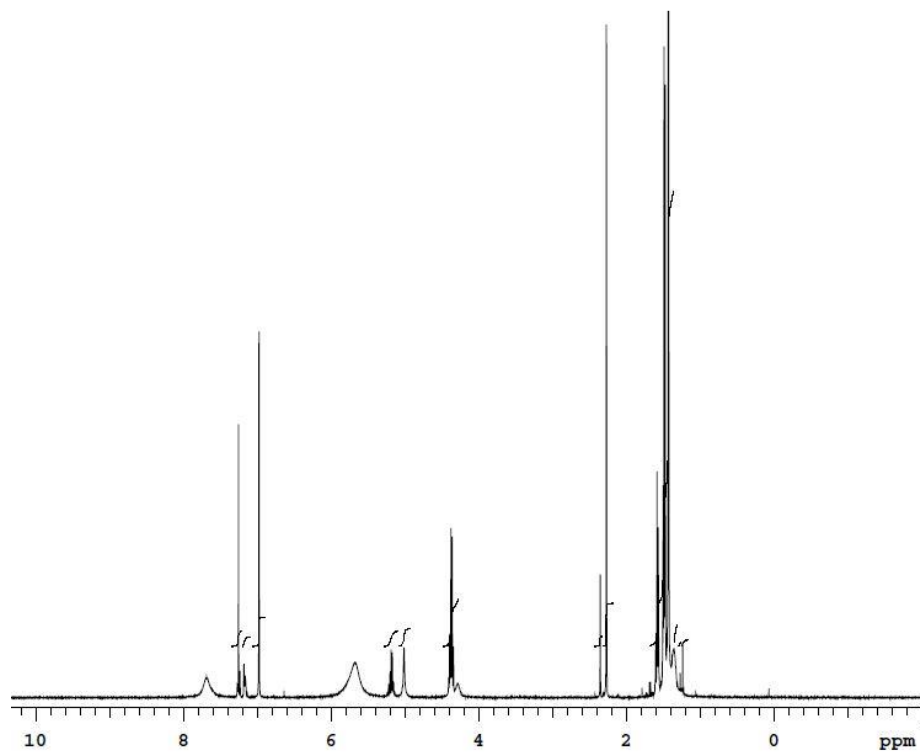


Figure E6. Proton NMR spectrum for experiment number 23 with azeotropic distillation.

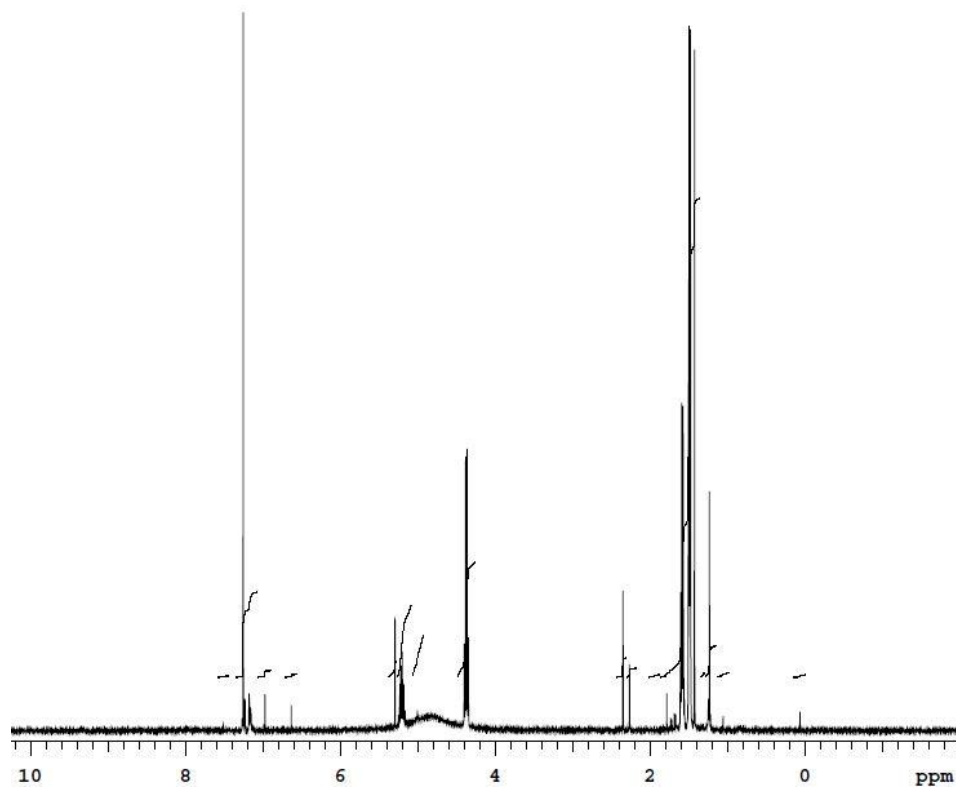


Figure E7. Proton NMR spectrum for first sample for reliability of NMR spectrums.

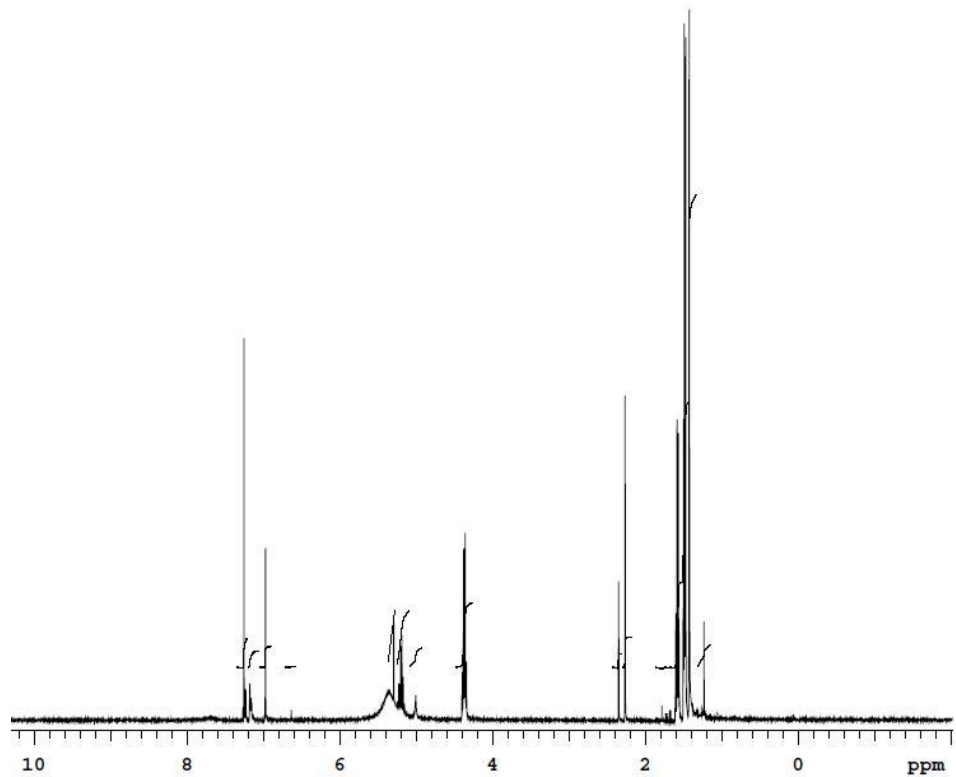


Figure E8. Proton NMR spectrum for second sample for reliability of NMR.

Appendix F. Attempt of replacing toluene with 2-MeTHF with azeotropic distillation

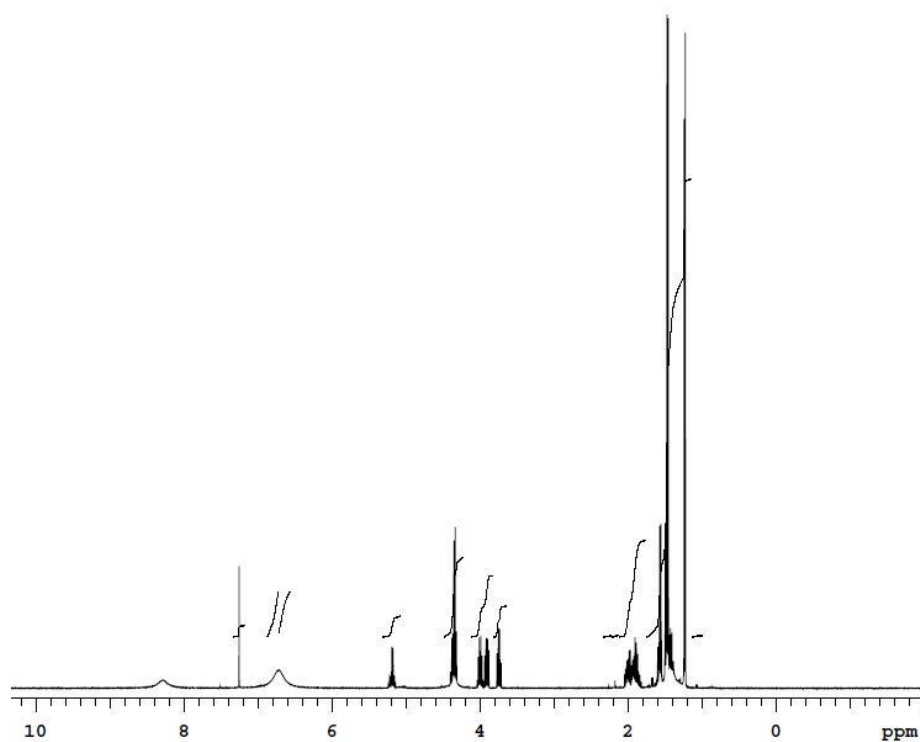


Figure F1. Proton NMR spectrum for attempt with 2-MeTHF as solvent with Na₂CO₃.

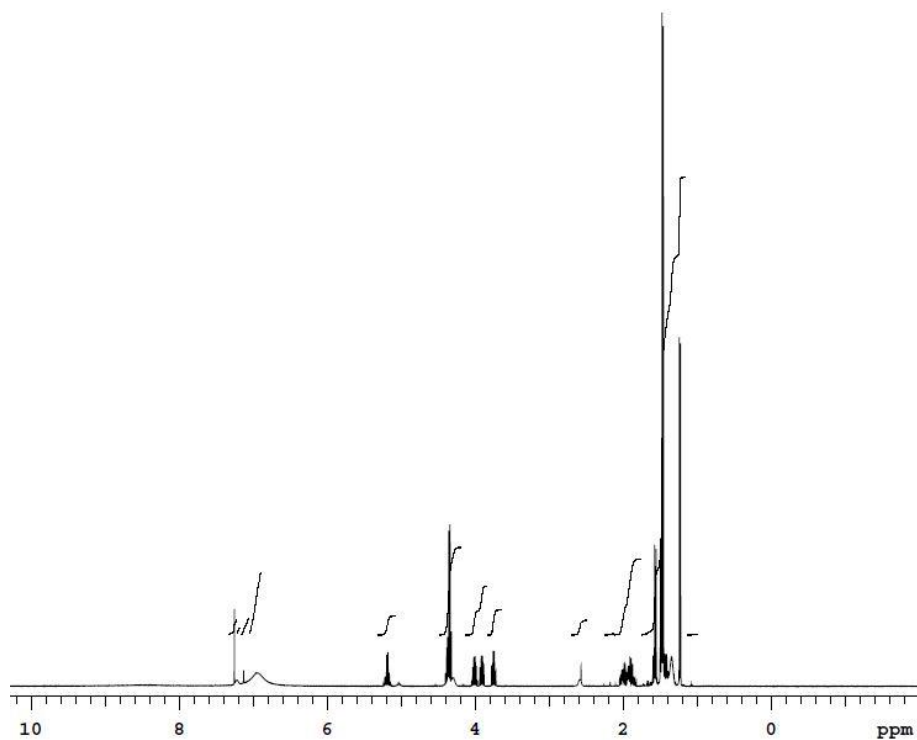


Figure F2. Proton NMR spectrum for attempt with 2-MeTHF as solvent with 2-methylimidazole.

Appendix G. Reference spectra

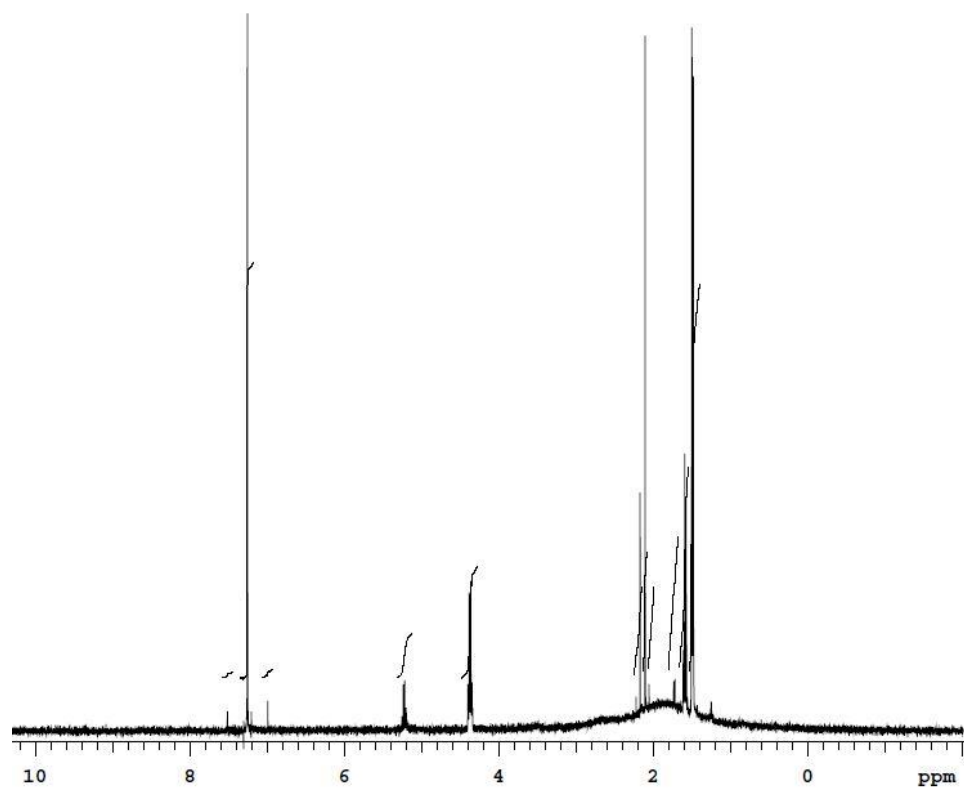


Figure G1. Proton NMR of the L-lactic acid used for all synthesis.