University of Texas Rio Grande Valley
ScholarWorks @ UTRGV

Theses and Dissertations

12-2020

The DMAP-Catalyzed Acylation of Alcohol -- A Mechanistic Study

Tania Veronica Alvarez Castro
The University of Texas Rio Grande Valley

Follow this and additional works at: https://scholarworks.utrgv.edu/etd

 Part of the Chemistry Commons

Recommended Citation

Alvarez Castro, Tania Veronica, "The DMAP-Catalyzed Acylation of Alcohol -- A Mechanistic Study" (2020). *Theses and Dissertations*. 608.
https://scholarworks.utrgv.edu/etd/608

This Thesis is brought to you for free and open access by ScholarWorks @ UTRGV. It has been accepted for inclusion in Theses and Dissertations by an authorized administrator of ScholarWorks @ UTRGV. For more information, please contact justin.white@utrgv.edu, william.flores01@utrgv.edu.

THE DMAP-CATALYZED ACYLATION OF ALCOHOLS – A MECHANISTIC STUDY

A Thesis

by

TANIA VERONICA ALVAREZ CASTRO

Submitted to the Graduate College of
The University of Texas Rio Grande Valley
In partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE

December 2020

Major Subject: Chemistry

THE DMAP-CATALYZED ACYLATION OF ALCOHOLS – A MECHANISTIC STUDY

A Thesis
by
TANIA VERONICA ALVAREZ CASTRO

COMMITTEE MEMBERS

Dr. R. Erik Plata
Chair of Committee

Dr. Arnulfo Mar
Committee Member

Dr. Jason Parsons
Committee Member

Dr. Evangelia Kotsikorou
Committee Member

December 2020

Copyright 2020 Tania Veronica Alvarez Castro
All Rights Reserved

ABSTRACT

Alvarez Castro, Tania Veronica, The DMAP-Catalyzed Acylation of Alcohols – A Mechanistic Study. Master of Science (MS), December 2020, 39 pp., 12 tables, 20 figures, references, 24 titles.

The mechanistic studies of Acylation of Alcohols catalyzed by 4-(N,N- Dimethyl-amino)-pyridine (DMAP) has been heavily studied in the literature. This reaction has attracted considerable interest from the synthetic and mechanistic points of view in recent years. In this research, the acylation of alcohols is prepared from cyclohexanol and acetic anhydride that is catalyzed by DMAP using triethyl amine (NEt_3) as the auxiliary base and dichloromethane (DCM) as solvent. The reaction and final product will be analyzed by using gas chromatography (GC) and reaction progress kinetic analysis (RPKA). The mechanistic insights obtained in the present study should be useful for understanding the acylation of alcohols, and hence, provide valuable information.

DEDICATION

I would like to dedicate this to my siblings, Michelle and Victor for all of their support throughout these years, y por siempre mantenerme en mi camino ninja. To my parents Veronica and Victor who always taught us the importance of education and made their best effort to give it to us ever since children. To my love Juan Lopez, for all of his patience, support, and love, someone who is always by my side with every struggle I encounter and never stopped believing in me. To my friend Michael Carrillo, thank you for your support, your words of guidance, and I will always cherish all the adventures that we have shared with many more to come.

The completion of my studies would have never been possible without your love. Thank you all for always believing in me. I love you all.

ACKNOWLEDGMENTS

I would like to thank my research advisor, Dr. R. Erik Plata, for your support and help during these years in my master's degree. I am so grateful for your advice, sharing your knowledge, and your patience towards me.

I would like to thank my committee members, Dr. Evangelia Kotsikorou, Dr. Arnulfo Mar and Dr. Jason G. Parsons; to all the professors that help me throughout my whole career since my bachelor's degree until now my master's degree, for every word of advice, for their knowledge, and for their support, thank you to each one of you.

Lastly, to my research lab partner, Samaris Ortega, who was always there supporting me since the beginning; helping each other when we encounter any struggle while doing research. To all the personnel and lab friends in the Chemistry Department at Brownsville campus; for all your guidance and help with all the questions and problems I had that allowed me to complete my work. Thank you all.

I want to acknowledge, as an international student, to my second family; thank you to each one of my international friends who gave me support in different aspects that I needed while being in the states. Words cannot express my deepest gratefulness to all of you, thank you a lot!

TABLE OF CONTENTS

LIST OF TABLES

Page

LIST OF FIGURES

Page

CHAPTER I

INTRODUCTION

Organic chemistry is defined as an elemental part of chemistry that focuses on the study of compounds that are composed of carbons; sometimes combined only with hydrogen, and in occasions, with oxygen and nitrogen (C, H, O, N). With organic compounds, carbon atoms can form strong bonds to other carbon atoms, forming rings and chains of carbon atoms. We use carbon atoms in our favor to provoke chemical reactions and study both their chemical reactivity, and the electron flow. This furthers the understanding of reaction mechanisms and entices the proposal of new mechanisms.

A mechanism describes the sequence of elementary reactions that must occur to go from reactants to products.[1] It follows four steps: nucleophilic attack which is the nucleophile attacking the electrophile, the arrow pushing of one curve by the loss of leaving group, proton transfer that is characterized by two curve arrows, and rearrangements.[2]

By exploring these factors, we will focus in one specific general mechanism: "Fisher Esterification" being the general knowledge of the reaction of the proposed abstract: Acylation of Alcohols mechanism.

Fisher Esterification

Esters are the result of an acid infused with an alcohol, eliminating the byproduct being water. In this general reaction, a carboxylic acid group combines with the hydroxyl group of an alcohol. The reaction, which takes place in the presence of an acid catalyst, produces an ester and water. The ester product is favored when an excess of acid or alcohol is used.[3]

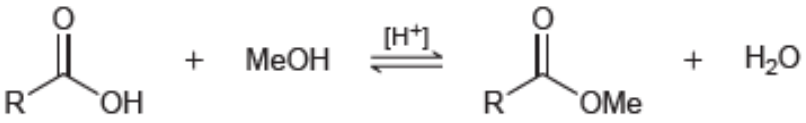

Figure 1. Fisher esterification reaction.

Esterification in a presence of an acid presents another advantage: not only does it increase the reaction rate, but it improves the performance of the equilibrium displacement in the process of forming the ester. Another aspect to consider with Fisher esterification reaction is the influence from the nature of an alcohol. Alcohols are distinguished by their performance and their esterification rate. That performance is depended on if the alcohol is classified as a primary, secondary, or tertiary.

Primary alcohols can be esterified faster than secondary ones, whereas, tertiary alcohols could be faster than secondary ones, and possibly even exceed primary ones. Taking all of this into consideration, it can reveal a difference in the mechanism. In esterification, the separation of an alcohol molecule could occur, and its observation in the mechanism is done by inspecting the isotope of oxygen (^{18}O) from the alcohol. Primary and secondary alcohols have the isotope

localized in the ester while tertiary alcohols have it in the byproduct water. Figure 2 shows the accepted mechanism of what to expect from a nucleophilic acyl substitution that takes under acidic conditions.

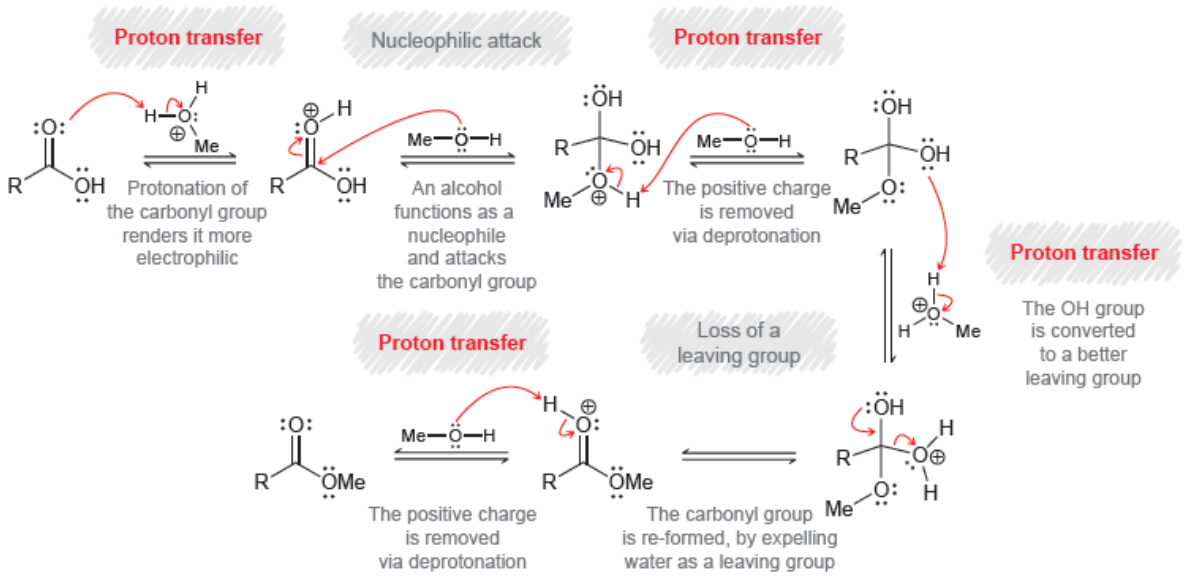

Figure 2. Fisher esterification mechanism.

Acylation of Alcohols Catalyzed by DMAP

The acylation of alcohols is one of the important and routinely utilized transformations in organic synthesis. [4] and the acylation of cyclohexanol with acetic anhydride catalyzed by 4-(dimethylamino)pyridine (DMAP) has been studied in this thesis. The acyl group serves as an important protecting group for alcohols because of its stability toward a variety of reagents.[5] 4-(N,N-Dimethylamino)pyridine (DMAP) is a very effective nucleophilic base catalyst for the esterification of alcohols with acid anhydride[6-8] and other related reactions[9,10]. An advantage of the acylation of the DMAP catalyst with anhydride is that alcohols are less reactive than them

since anhydrides have a reactivity higher than carboxylic acids. Esterification of alcohols using acid anhydrides in pyridine has been known and extensively used by organic chemists for nearly 100 years.[11] In 1969 Steglich and Hofle published the now standard method of catalyzing the acylation of alcohol by DMAP.[6b, 7a] In figure 3, it shows the consensus mechanism for DMAP-catalyzed acylation reaction where the pathway goes to the nucleophilic attack of DMAP at the carbonyl group from the anhydride, and later on forming the acylpyridinium ion pair. Lastly, this ion pair reacts with the alcohol that yields the final product.

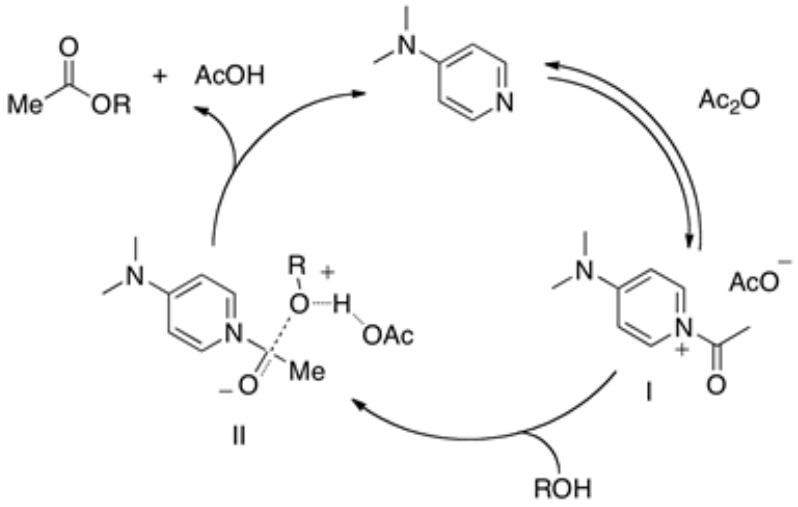

Figure 3. The consensus mechanism for DMAP-catalyzed acylation.

However, a recent review of the mechanistic characteristics of this reaction highlighted the importance of the deprotonation step as well as the influence of the auxiliary base on the catalytic activity of DMAP.[12] Recently, Zipse and co-workers proposed a mechanism for the DMAP-catalyzed acetylation of alcohols (Figure 4).[13a]

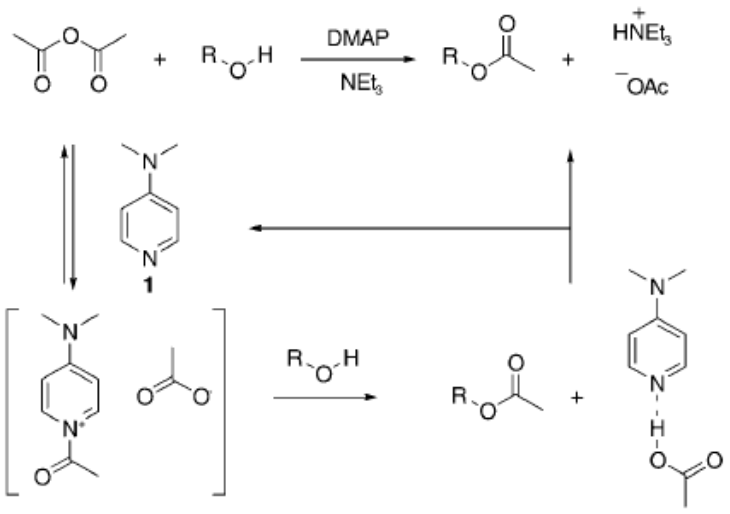

Figure 4. DMAP-catalyzed reaction with triethylamine (NEt_3)

This mechanism involves the formation of the acylpyridinium ion pair from the reaction of the DMAP catalyst with the acyl donor; later, the alcohol reacting with the acylated catalyst in the rate-determining second step and forming the ester product with the protonated catalyst. The regeneration of the last one required the auxiliary base such as triethylamine.

4-(Dimethylamino)pyridine (DMAP) is a catalyst of out-standing utility in a variety of group-transfer reactions, such the acylation of alcohols and amines. [6, 7a-c,e, 14-17] In this thesis, the kinetics of the DMAP-catalyzed reaction of acetic anhydride with cyclohexanol was studied with the alcohol in dichloromethane (DCM) at room temperature in the presence of triethylamine (NEt_3) as the auxiliary base.

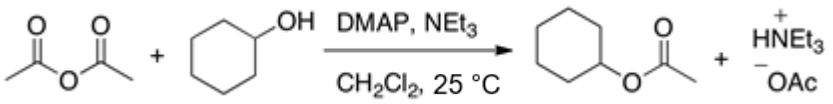

Figure 5. DMAP – Catalyzed acylation reaction of cyclohexanol with acetic anhydride using triethyl amine as the auxiliary base and dichloromethane as solvent.

Furthermore, the role of the catalyst, reagents, and product of the reaction was examined. The study of the auxiliary base which has been said that it does not play any role in the reaction, however, it might contribute with some part of the reaction. It utilized a combination of the Gas Chromatography (GC) and Reaction Progress Kinetic Analysis (RPKA).

Gas Chromatography

Gas chromatography (GC) is an analytical technique that separates and analyzes compounds by vaporizing them, and it analyzes them without decomposition based on their boiling points and other properties. The GC is a technique used in many environmental and forensic laboratories. Samples can be analyzed if the compounds are sufficiently thermally stable and reasonably volatile.[18]

Figure 6. Thermo Scientific Trace 1310 Gas Chromatography

GC System Configuration

The process is initiated by collecting and injecting the sample, usually in liquid form, by using a syringe and into to a box identified as the GC Injector. From there, the sample is vaporized into a gas phase. In this stage, the mixture could be composed of one or more different kinds of gases. When the sample in its gas phase is injected, it meets with the mobile phase known as the inert carrier gas such as nitrogen, helium, or hydrogen. The carrier gas is inert to avoid any reaction with the sample mixture. Subsequently, the sample mixture will get heated up and will travel through a long tube called the column.

The column is a long length of tube that is coiled inside the column oven, and it is referred to as the stationary phase on some occasions. Its purpose is to separate compounds from a sample mixture; a factor to consider with the column is that the longer the tube, the better the separation. After the sample mixture travels throughout the column, it will arrive at the GC detector that identifies particles from the sample mixture. The GC detector receives the particles at different rates and displays signals that can be analyzed on a computer. Those signals are called chromatogram.

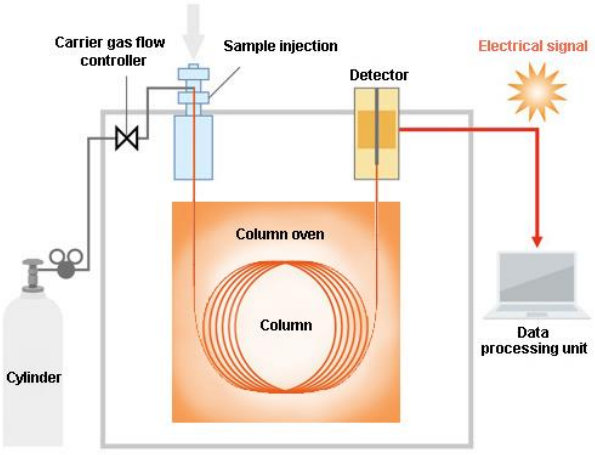

Figure 7. GC System Configuration[19]

GC Separation

In detail, the stationary phase is a packed column that is coated along its sides with the liquid stationary phase. When the sample mixture and the mobile phase interacts and travels throughout the stationary phase, the mixture starts to separate at different rate times based on the boiling point of each compound from the mixture since compounds with higher boiling points tend to travel closer to the liquid stationary phase.

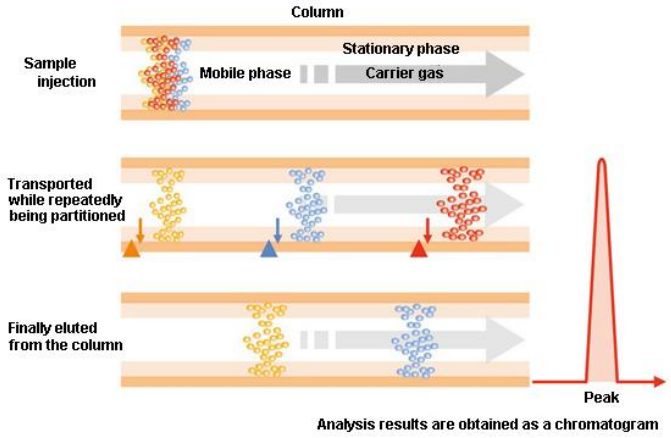

Figure 8. GC Separation[19]

When the sample reaches the GC detector and displays a chromatogram with peaks (signals), the first peak usually displayed is the solvent that was used to dissolve the sample mixture due to their low boiling points. The following peaks on the chromatogram display the specific compounds from the sample mixture.

Another aspect to consider is the different rates of the compounds come out on the chromatogram. Commonly, first it displays the baseline where nothing is detected. The next peak after the solvent usually is a compound that has a low boiling point within the whole sample mixture. Low boiling point compounds vaporize quickly, and they travel fast throughout the

column (stationary phase) because they like to interact with the gas or mobile phase. The other peaks from the chromatogram are usually compounds with higher boiling point since they spend more time in the stationary phase.

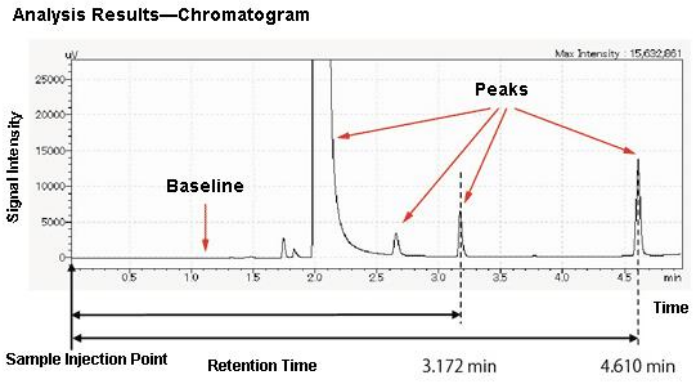

Figure 9. GC Chromatogram[19]

The chromatogram is a plot of signal intensity (y-axis) versus retention time (x-axis). The intensity represents the particles displayed by the detector at specific times. Based on the retention time (RT) of each peak, one can tell if a sample is smaller with a low boiling point or bigger with a higher boiling point. To know the identity of each individual compound, usually it is needed to run a reference beforehand, then match the retention time afterwards. Another aspect to consider while analyzing the GC spectrum is to look at the difference between the peaks allowing to compare compounds qualitatively; also, quantitatively where the area of each peak is directly proportional to the amount of the compound.

To explore this point in a quantitative fashion, in this thesis, the area of each peak from the GC spectrum was analyzed. The area of each peak allowed to calculate the kinetics of each experiment by following the reaction progress kinetics analysis (RPKA).

Reaction Progress Kinetic Analysis

The reaction progress kinetic analysis (RPKA) was developed by Pr. Donna Blackmond. This kinetic analysis approach simplifies kinetic studies of organic reactions. It helps chemists process the development and optimize reactions faster, investigate catalyst performance, and ensure process robustness. RPKA determines rate laws and elucidates significant information to the reaction mechanism. It can give the same information that classical kinetic approaches give with considerably less experiments required.

RPKA works with continuous accurate method of experimental data collection [20]; using the Gas Chromatography (GC) as an example. The use of this analysis begins by choosing a set of reaction conditions for the first experiment, and it will be considered as standard conditions where it will be decided the initial concentrations for the substrates and concentration of catalyst; as well choosing a fixed temperature that stays constant throughout all the experiments. From here, following reactions will be allowed to have alterations from these conditions. Experimentally, these alterations are known as protocols: Different Excess and Same Excess.

Different Excess tells the order in substrate(s). Several reactions are carried out with different values from the standard conditions. The main goal with this protocol, by plotting the data in graphical rate equation, is to identify if the data overlay in any different form and to help if the reaction exhibits simpler integer order, or if it exhibits saturation kinetics in one or both of the two substrates.[21] Same Excess reveals catalyst robustness or product inhibition. Moreover, same excess follows the standard conditions but having different values of the starting concentrations of the substrates. Ideally, plotting this data in graphical rate equation would show if the curves overlay or not, demonstrating that catalyst or product inhibition is not a feature in the set reactions. The data gives a handle where to look next, or the design next set of

experiments. This data can be shown by drawing out a reaction mechanism or constructing an energy diagram. With the data given by the GC, the following equation 1 is applied to get the graphical rate equation:

$$\%\ Conversion = \frac{Area\ of\ Product}{Area\ of\ Starting\ Material + Area\ of\ Product} * 100 \qquad (1)$$

First, it is needed to get the percent conversion by getting quantitatively the area of the peak from the starting material (SM) and area of the peak from the product in the GC spectrum. From there, the concentration is obtained using the following equation 2:

$$Concentration = \frac{100 - \%\ Conversion}{100} * ([SM]) \qquad (2)$$

where [SM] stands for the concentration used as the starting material in the initial reaction. Finally, the graphical rate equation is set up as concentration vs time (min).

RPKA, in general, is ideal because when having classical kinetic studies that can only give a general summary of the journey that molecules take, RPKA allows more to learn by following the molecules themselves on their journey.

Objective

Several things like the role of the DMAP catalyst, the reagents cyclohexanol (alcohol) and acetic anhydride; and the role of the auxiliary base triethylamine and the product were considered in here. Table 1 enlists the properties of the reagents used in this research.

	MW	Density	Melting Point	Boiling Point
	g/mol	g/mL	°C	°C
cyclohexanol	100.16	0.948	25.4	160.80
acetic anhydride	102.09	1.08	-73.4	139.50
DMAP cat.	122.17		110.0	162.00
triethylamine	101.19	0.726	-114.7	89.30
biphenyl (int. std.)	154.21	1.04	69.00	256.10
DCM	84.93	1.34	-95.1	39.750

Table 1. Reagent table for the acylation of alcohols reaction.

Studying the reaction progress kinetic analysis, we were able to look at the order of the catalyst. The common questions were if there was something inhibiting the catalyst, if it decomposed with time, if it was stable, or in general, what was happening to it; what happened to the catalyst after one turnover, two turnovers or fifty turnovers. For the byproducts and product inhibition, we wanted to know if it slowed down or if it sped up. The order of the substrates was decided to explore the order of the reagents, catalyst stability and product acceleration. To understand all this, two protocols were needed to be followed: different excess and same excess.

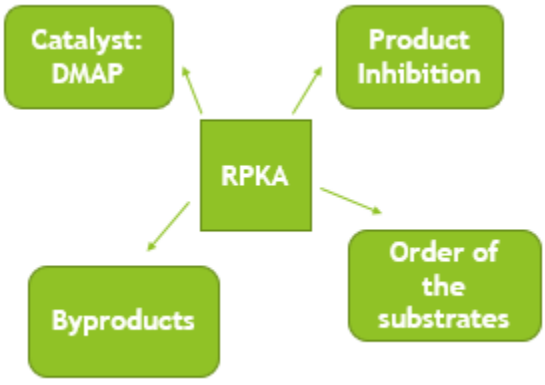

Figure 10. Studying the reaction progress kinetic analysis.

CHAPTER II

MATERIALS AND METHODS

The present study was performed in the Department of Chemistry of The University of Texas Rio Grande Valley. The detail of materials used, methodologies employed, experiments and techniques have been elaborated below.

Stock Solutions Preparation

All the chemicals used were of analytical grade. Each reagent was commercially available and used without further purification. Stock solutions were freshly prepared with dichloromethane (DCM) solvent at room temperature (25 ℃) and stocked in several volumetric flasks. All the stock solutions were diluted to the required concentrations needed in each of the studies.

Each reagent has a standard concentration. From there, the different excess and same excess protocols were applied to understand the kinetics of each reagent at different concentrations.

Standard Concentrations	Concentration M	[excess] M
cyclohexanol	0.100	0.010
acetic anhydride	0.110	
DMAP cat.	0.002	
triethylamine	0.150	0.050
biphenyl (int. std.)	0.025	
DCM		

Table 2. Standard concentrations for each reagent.

4-Dimethylaminopyridine (DMAP) stock solution

A 0.02 M solution of DMAP catalyst was prepared by dissolving 610.9 mg in a 250 ml volumetric flask with DCM solvent.

Cyclohexanol stock solution

A 1 M solution of cyclohexanol was prepared by dissolving 1001.6 mg in a 10 ml volumetric flask with DCM solvent.

Biphenyl (internal standard) stock solution

A 0.25 M solution of biphenyl was prepared by dissolving 385.5 mg in a 10 ml volumetric flask with DCM solvent.

Triethylamine stock solution

A 1.5 M solution of triethylamine was prepared by dissolving 1517.9 mg in a 10 ml volumetric flask with DCM solvent.

Acetic anhydride stock solution

A 1.1 M solution of acetic anhydride was prepared by dissolving 1123.0 mg in a 10 ml volumetric flask with DCM solvent.

Preparation of Each Reaction

Each reaction, following the different protocols, was prepared side-by-side in a scintillation vial with a total volume up to 10 milliliters between two to six hours. Reactions were performed under standard conditions at 25 ℃ and stirred with a small octagon magnetic stirring bar inside the vial by using a Thermo Scientific hot plate stirrer. In the preparation of each vial, solutions were added by using a syringe.

In all cases studied, the reactions have been performed by mixing stock solution of Cyclohexanol as the alcohol and the internal standard Biphenyl. Next, the DCM solvent, the auxiliary base Triethylamine and the DMAP catalyst were added in the same order. Finally, to start the reaction, the acetic anhydride was added at time zero. Aliquots were taken out, and diluted in a GC vial filled with DCM, at specific data points every five minutes for thirty minutes; then an aliquot was taken out every hour until completing either between two to six hours of reaction time. All kinetic measurements were performed by using Gas Chromatography.

Figure 11. Scintillation vial with the prepared reaction

Kinetic Measurements

Different excess cyclohexanol

The standard reaction was 0.10 M for the alcohol Cyclohexanol and 0.11 M for the acetic anhydride having an excess of 0.01 M; 0.15 M for the triethylamine, and 0.002 M for DMAP catalyst. (Table 2)

The different excess of Cyclohexanol, the alcohol was 0.05 M and 0.11 M for the acetic anhydride with an excess of 0.06 M. Both reactions were stirred, and aliquots were taken out for two hours.

dea	Concentration	[excess]
Cyclohexanol	M	M
cyclohexanol	0.050	0.060
acetic anhydride	0.110	
DMAP cat.	0.002	
triethylamine	0.150	0.100
biphenyl (int. std.)	0.025	
DCM		

Table 3. Different excess in Cyclohexanol

Different excess acetic anhydride

The standard reaction was 0.10 M for the alcohol Cyclohexanol and 0.11 M for the acetic anhydride having an excess of 0.01 M; 0.15 M for the triethylamine, and 0.002 M for DMAP catalyst. (Table 2)

The different excess of Acetic Anhydride, the cyclohexanol was 0.10 M and 0.22 M for the acetic anhydride with an excess of 0.12 M. Both reactions were stirred, and aliquots were taken out for two hours.

deb	Concentration	[excess]
Acetic Anhydride	M	M
cyclohexanol	0.100	0.120
acetic anhydride	0.220	
DMAP cat.	0.002	
triethylamine	0.150	0.050
biphenyl (int. std.)	0.025	
DCM		

Table 4. Different excess in Acetic Anhydride

Different excess triethylamine

In different excess of TEA, the standard reaction for the alcohol and the acetic anhydride stays the same; only changing the concentration of the auxiliary base (Table 2). Both reactions were stirred, and aliquots were taken out for two hours.

dec	Concentration	[excess]
Triethylamine	M	M
cyclohexanol	0.100	0.010
acetic anhydride	0.110	
DMAP cat.	0.002	
triethylamine	0.300	0.200
biphenyl (int. std.)	0.025	
DCM		

Table 5. Different excess in Triethylamine

Same excess

Same excess allows to see if there is something happening with the catalyst by keeping the same concentration of the catalyst and changing the concentration of the reagents.

In same excess for the standard reaction was 0.10 M for the cyclohexanol and 0.11 M for the acetic anhydride, having an excess of 0.01 M. Another reaction was performed with 0.08 M for the cyclohexanol, and 0.09 M for the acetic anhydride having an excess of 0.01 M. Both reactions were stirred, and aliquots were taken out for two hours.

Same	Concentration	[excess]
Excess	M	M
cyclohexanol	0.080	0.010
acetic anhydride	0.090	
DMAP cat.	0.002	
triethylamine	0.150	0.070
biphenyl (int. std.)	0.025	
DCM		

Table 6. Same Excess

Different concentrations Triethylamine

The standard reaction was 0.10 M for the alcohol Cyclohexanol and 0.11 M for the acetic anhydride having an excess of 0.01 M; 0.15 M for the triethylamine, and 0.002 M for DMAP catalyst. (Table 2)

For these reactions, the Triethylamine was studied with different concentrations:

Different Concentration triethylamine	Concentration M	[excess] M
cyclohexanol	0.100	0.010
acetic anhydride	0.110	
DMAP cat.	0.002	
triethylamine	0.150	0.050
biphenyl (int. std.)	0.025	
DCM		

(1)

Different Concentration triethylamine
No NEt_3 [0.0 M]
0.15 M
0.05 M
0.025 M
0.0125 M
0.006 M

(2)

Different Concentration triethylamine
0.050 M
0.045 M
0.040 M
0.035 M
0.030 M
0.025 M

Table 7. Different Concentrations Triethylamine

All the reactions were stirred, and aliquots were taken out every five minutes for thirty minutes.

Different concentrations Acetic Anhydride

The standard reaction was 0.10 M for the alcohol Cyclohexanol and 0.11 M for the acetic anhydride having an excess of 0.01 M; 0.15 M for the triethylamine, and 0.002 M for DMAP catalyst. (Table 2)

For these reactions, the Acetic Anhydride was studied with different concentrations:

Different Concentration Acetic Anhydride
0.50 M
0.11 M
0.22 M

Table 8. Different Concentrations Acetic Anhydride

The three reactions were stirred, and aliquots were taken out for four hours and a half.

Same Excess Cyclohexanol and Acetic Anhydride

In same excess for the standard reaction was 0.10 M for the cyclohexanol and 0.11 M for the acetic anhydride, having an excess of 0.01 M. Other reactions were performed:

Same Excess	
Cyclohexanol	Acetic Anhydride
0.10 M	0.11 M
0.08 M	0.09 M
0.05 M	0.06 M
0.025 M	0.035 M
0.010 M	0.011 M

Table 9. Same Excess Cyclohexanol and Acetic Anhydride

All reactions were stirred, and aliquots were taken out for six hours.

Different concentrations 4-Dimethylaminopyridine (DMAP) catalyst

The standard reaction was 0.10 M for the alcohol Cyclohexanol and 0.11 M for the acetic anhydride having an excess of 0.01 M; 0.15 M for the triethylamine, and 0.002 M for DMAP catalyst. (Table 2)

For these reactions, the DMAP catalyst was studied with different concentrations:

Different Concentration DMAP
No DMAP
0.002 M
0.001 M

Table 10. Different concentrations DMAP-catalyst

Characterization

Characterization of materials were performed by using a Gas Chromatography (GC) technique with a Thermo Scientific GC Column TG-5MS:

Thermo Scientific	
Column	TG-5MS
Length	30m
I.D.	0.32mm
Film	0.25 µm
Max. Temp.	330/350 °C
P/N	26098-1430
S/N	1471657

Table 11. GC Column information

GC Method			
Sampler		**GC Detector**	
Draw speed	Slow	**Detector type**	Flame Ionization Detector (FID)
Fill strokes	5	**Signal settings**	
Air volume	1.00 µl	Acquisition on	0.000 min
Sample depth	Bottom	Acquisition off	10.000 min
GC Inlets		Data collection rate	10 Hz
Temperature	275 °C	**Detector temperature**	350 °C
Operating mode	Splitless	**Flame**	
Split flow	55.0 ml/min	Ignition threshold	1.0 pA
Splitless time	1.00 min	Peak width	Standard
Purge flow	5.00 ml/min	**Gas Settings**	
Gas saver flow	10.0 ml/min	Air flow	350.0 ml/min
Gas saver time	1.50 min	Makeup gas flow	15.0 ml/min
		Hydrogen flow	35.0 ml/min

GC Oven Settings			
Prep Run Timeout	10.00 min		
Oven equilibration time	0.10 min		
Ready delay	0.00 min		
Retention Time [min]	**Rate [°C/min]**	**Target Value [°C]**	**Hold Time [min]**
0.000	Run	-	-
0.000	0.000	35.0	0.00
9.833	30.000	330.0	0.00
-	-	-	-
10.000	Stop Run	-	-

Table 12. Method used in GC

The implication of these findings for the kinetic resolution of each protocol are discussed in the following chapter.

CHAPTER III

RESULTS AND DISCUSSION

In the present results, the reaction progress kinetic analysis was investigated by using the gas chromatography. The kinetics of the reaction of cyclohexanol with acetic anhydride as catalyzed by 4(N,N-dimethylamino) pyridine (DMAP)/triethylamine have been studied at 25 °C.

Each graphical rate equation was calculated by using equation 1 and 2 (Refer Chapter I – Reaction Progress Kinetic Analysis). The advantage of Reaction Progress Kinetic Analysis (RPKA) requires fewer experiments. To obtain these results, the area of the peak was needed from the starting material and the product. Every aliquot taken at specific times showed a consumption from the starting material meaning that the substrate concentration changes simultaneously throughout the reaction. From here, the behavior of the reaction based on the protocols was observed.

Different Excess Cyclohexanol

In this reaction, the standard concentration of cyclohexanol is 0.10 M and 0.11 M for acetic anhydride. Now, the different excess for the second reaction is that cyclohexanol concentration was cut in half, having a 0.05 M and an excess of 0.06 M, but acetic anhydride keeping the same concentration. Based on the graphical rate equation, the different excess of cyclohexanol reaction illustrates a faster reaction considering that cyclohexanol concentration is in half. A factor in this reaction is that acetic anhydride is known as strong substance, and considering that it starts the

reaction, having less in one of the substrates allows it to domain and finishing the reaction faster compared to the standard conditions. This protocol would be considered positive order kinetic reaction.

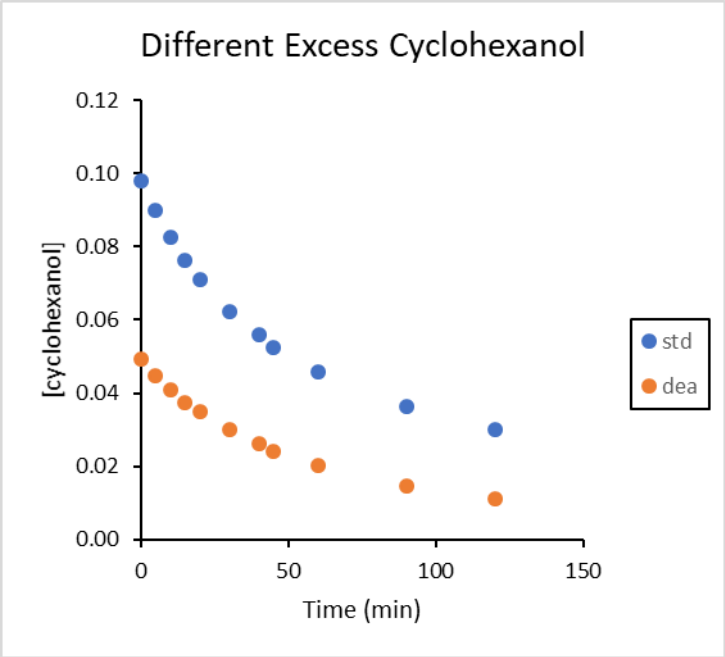

Figure 12. Different excess of cyclohexanol: Standard 0.10 M, Dif. Excess 0.05 M.

Different Excess Acetic Anhydride

In this protocol, the standard concentrations are the same, but now with the difference of acetic anhydride that the concentration is 0.22 M with an excess of 0.12 M. Based on the graph, both reactions started at the same rate; however, it appears that after 20 minutes the different excess reaction became faster. Looking at the plot, it can be said that the reaction is positive order as Acetic Anhydride is chosen in large excess over the other.

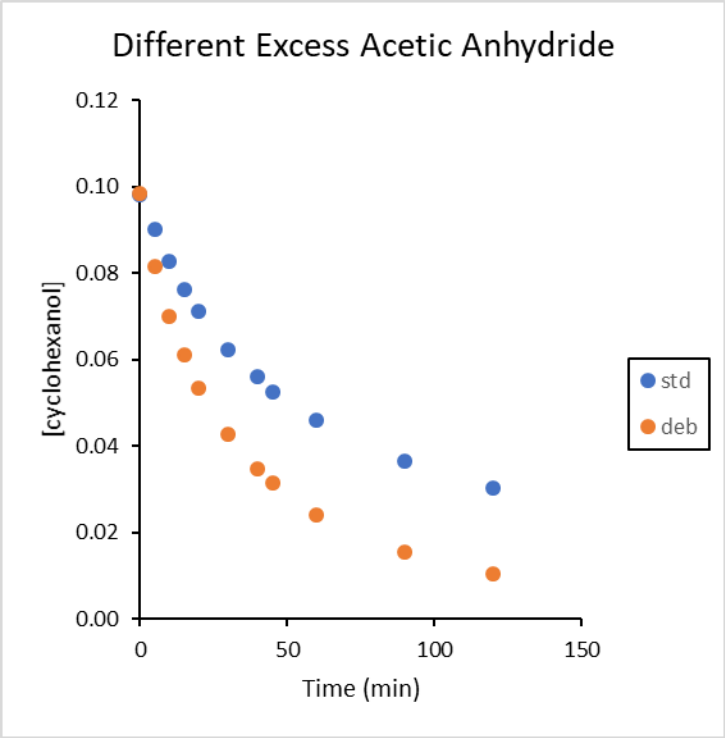

Figure 13. Different excess of acetic anhydride: Standard 0.11 M, Dif. Excess 0.22 M.

Different Excess Triethylamine

In this protocol, the concentration of the auxiliary base was changed. It has been said that the auxiliary base has no influence on the reaction rate on the DMAP-catalyzed reaction with the cyclohexanol and acetic anhydride. In this case, for this reaction with the same standard conditions, and the excess of the triethylamine being 0.30 M, the closer the data on the graph are to horizontal line, the closer the reaction is to zero order kinetics. However, it appears that after fifteen minutes, the auxiliary base did something in the reaction as the standard illustrates to be a little bit faster meaning that at lower concentrations, the auxiliary base might contribute in something during the reaction.

More studies with the auxiliary base are shown later on during these present studies.

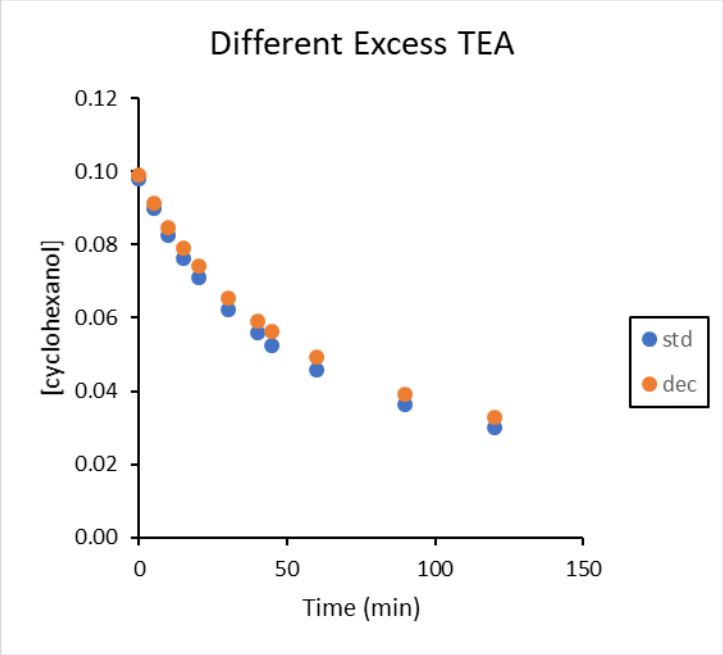

Figure 14. Different excess of triethylamine: Standard 0.15 M, Dif. Excess 0.30 M.

Same Excess

In same excess reaction, it has the same excess but different starting concentrations. Figure 15 illustrates that having the standard concentration of cyclohexanol 0.10 M and the other starting concentration of 0.08 M with same excess did not show any catalyst deactivation. In another words, when the two curves overlap, it confirms that the presence of the product or the extra work by the catalyst in the reaction did not have any influence in the reaction kinetics confirming that the reaction was zero order.

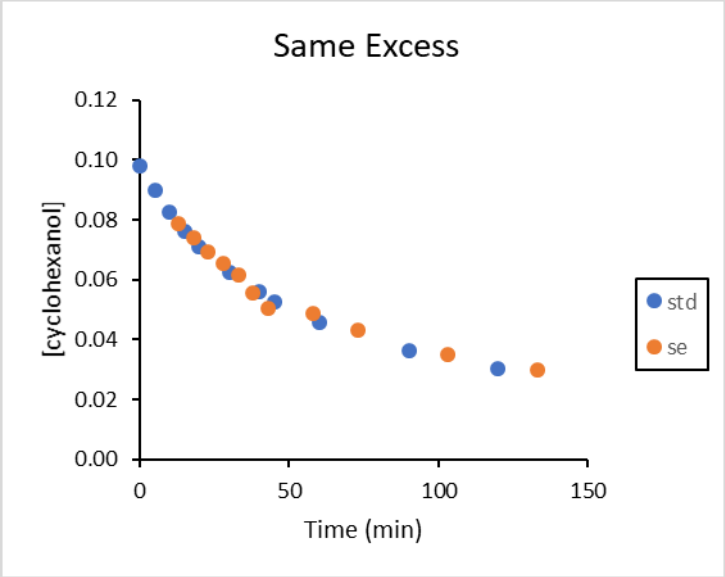

Figure 15. Same excess Cyclohexanol 0.1 M & 0.08 M. Acetic anhydride 0.11 M & 0.09 M

This reaction helps to understand the purpose of the DMAP-catalyst as well. Here it can be said that the catalyst deactivation has happened over time for the two separate reactions with different starting concentrations of the substrates but having identical values of the excess. In this case, choosing any concentration for the substrates but keeping same standard concentration of the catalyst, it can be said that the reaction with a higher concentration, which is the standard,

might contain more product compared with the lower initial concentration, and the catalyst for the reaction with higher concentration could have completed more turnovers. However, it is possible to say that the product and catalyst deactivation could slow the reaction over time.

Different concentrations Auxiliary Base – Triethylamine

The purpose of these several reactions was to observe if the auxiliary base has anything to do with extending the reaction. For all of them, the reactions lasted up to thirty minutes.

In figure 16, the first set of reactions were without the auxiliary base, the standard concentration 0.150 M, 0.050 M, 0.025 M, 0.0125 M and 0.006 M of triethylamine. Based on the graphical rate equation, between minute zero to ten, triethylamine does not contribute with anything on the reaction; giving the idea that it would be a zero-order reaction. However, after ten minutes the lower concentrations start making the reactions a little bit faster compared without the auxiliary base. It can be seen that reactions with 0.025 M and 0.050 M of the auxiliary base are faster than the rest of them. These findings illustrate that at some point the auxiliary base contributes in the reaction.

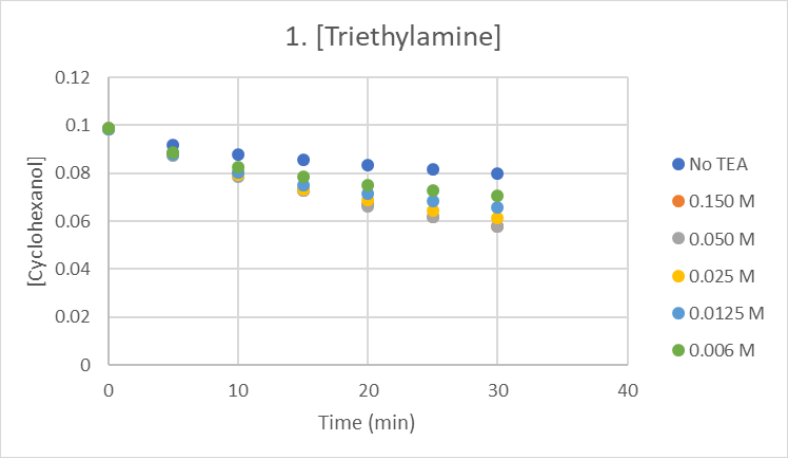

Figure 16. 1. [Triethylamine] reaction with concentrations of 0.015 M, 0.05 M, 0.025 M, 0.0125 M, 0.006 M and no Triethylamine at standard conditions for the substrates.

In figure 17, the reactions focused between the 0.050 M and 0.025 M of the triethylamine to see what happens in detail during the reaction. From the graphical rate equation, the data is closer to a horizontal line meaning that the reaction is zero-order kinetics. It has been said that the auxiliary base was found to have no influence on the reaction rate in earlier measurements on the DMAP-catalyzed reaction with cyclohexanol and acetic anhydride [13b], however as disproven in figure 16, it is shown that the reaction could be zero or first order. While concentrations between 0.050 M to 0.025 M from figure 17 demonstrated no greater significance in the reaction, the auxiliary base has shown that it does contribute to the reaction; by taking a closer look at the reaction without triethylamine from figure 16 that was going slower compared to the other ones. It is shown that between ten to twenty minutes in figure 16, the auxiliary base helps in the reaction, and perhaps after a specific time, it stops making any contribution.

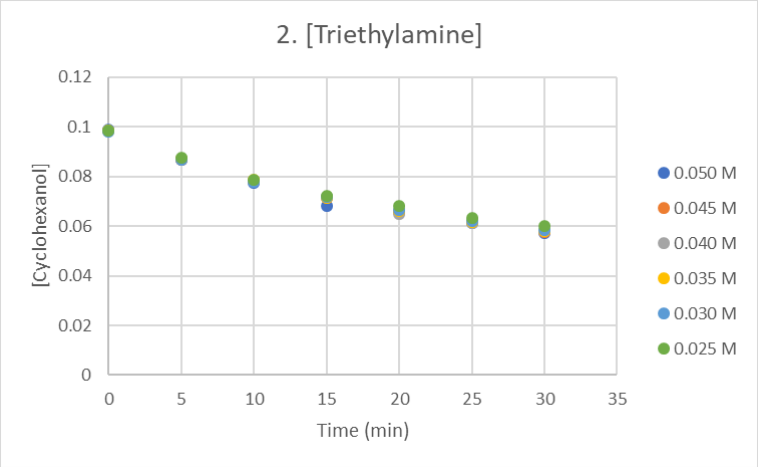

Figure 17. 2. [Triethylamine] with concentrations of 0.050 M, 0.045 M, 0.040 M, 0.035 M, 0.030 M, and 0.025 M at standard conditions for the substrates.

Different concentrations Acetic Anhydride

In these three reactions, it was studied the standard, double and half concentration of acetic anhydride by keeping the same standard concentration for the rest of the substrates. Acetic anhydride is a commonly used reagent in the presence of an acid or base catalyst, and it is the substrate that starts the reaction. In figure 18, the reactions carried out under three different sets of substrate conditions show that the higher concentration is the fastest one, so 0.22 M would be second order than the standard condition. However, the standard concentration 0.11 M of Ac_2O is faster than half concentration 0.50 M. Like it was mentioned before in different excess of Ac_2O, this is known as a strong substance and as it starts the reaction, it might decide how fast to go by starting its nucleophilic attack to the DMAP-catalyst and from there to speed up the reaction.

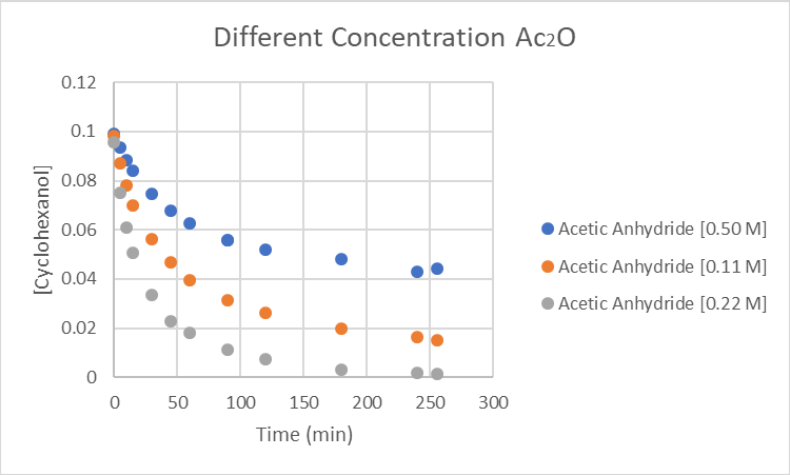

Figure 18. Different concentration Ac_2O: 0.50 M, 0.11 M & 0.22 M with the standard condition reaction.

Same Excess – Cyclohexanol and Acetic Anhydride

In past results, the same excess was already studied with cyclohexanol and acetic anhydride where the two reactions were the standard concentrations 0.10 M cyclohexanol, and 0.11 M Ac_2O versus 0.08 M cyclohexanol and 0.09 M Ac_2O; keeping the same excess. Now, further experiments were carried out with more different values of the standard concentrations. The purpose was to identify if the reaction stops at some point or if to continue through time; the reaction was set up for a duration of six hours.

The first reaction of vial 1 is the general standard concentration of cyclohexanol and acetic anhydride (Table 2). The second vial has a 0.08 M cyclohexanol and 0.09 M Ac_2O. The third vial has a 0.05 M cyclohexanol and 0.06 M Ac_2O. The fourth vial has a 0.025 M cyclohexanol and 0.035 M Ac_2O, and the last vial has a 0.01 M cyclohexanol and 0.011 M Ac_2O.

Figure 19 illustrates that having the standard concentration of cyclohexanol 0.10 M (vial 1) and the other starting concentration of 0.08 M (vial 2) with same excess did not show any catalyst deactivation as both almost overlap; but even as they almost overlap, both reactions could be second order. Reaction from vial 3 could fall into first order. Moreover, concentrations from vial 4 and 5 show a slower reaction that could be zero order reaction as the data is closer to horizontal line. The five curves end up overlaying after four hours, and it confirms that the catalyst deactivation or product inhibition is not a feature in these reactions; and the reactions stopped working around that time making them slower.

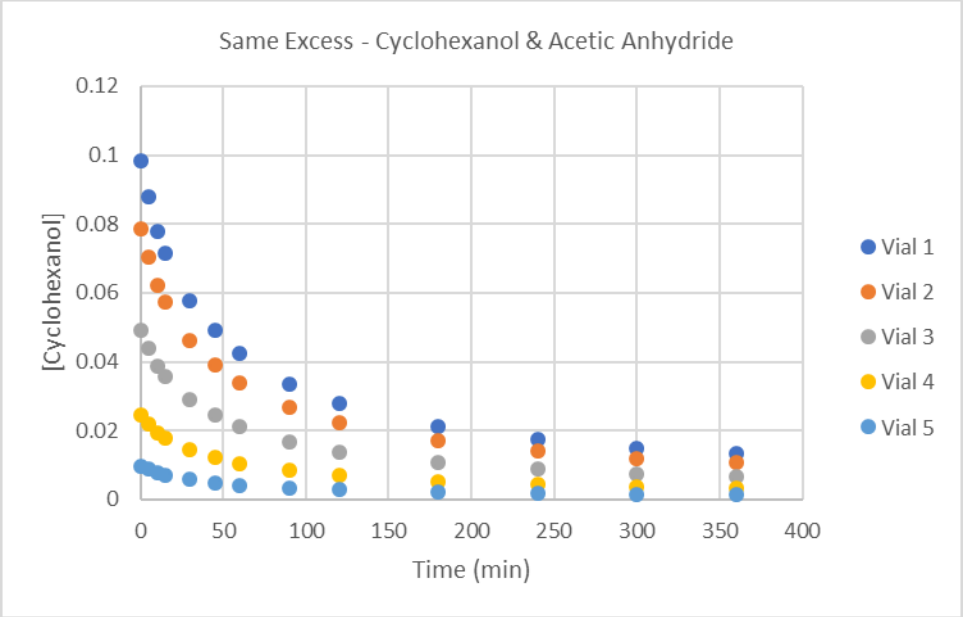

Figure 19. Same excess concentration of cyclohexanol and acetic anhydride. Vial 1: 0.10 M cyclohexanol and 0.11 M Ac_2O. Vial 2: 0.08 M cyclohexanol and 0.09 M Ac_2O. Vial 3: 0.05 M cyclohexanol and 0.06 M Ac_2O. Vial 4: 0.025 M cyclohexanol and 0.035 M Ac_2O. Vial 5: 0.01 M cyclohexanol and 0.011 M Ac_2O.

Different concentrations 4-Dimethylaminopyridine (DMAP) catalyst

In past studies, DMAP catalyst is observed in Same Excess reaction. The purpose was to obtain insight on the same catalyst standard concentration by having any concentration for the substrates but keeping the same excess. In these new reactions, the purpose was to look at different concentrations of DMAP catalyst but keeping the same standard concentration for the rest of the substrates. In previous studies of Same Excess, the catalyst did not show any catalyst deactivation. However, in these studies the first reaction without DMAP catalyst showed a horizontal line meaning a zero-order kinetic. The reaction by itself was too slow and can be said that up to the point of six hours, there was minimal consumption of the substrate and no formation of the product.

For the second reaction, the standard concentration of 0.002 M DMAP resulted in a faster reaction. The results can illustrate that after four hours, there was already more product present and no catalyst deactivation. DMAP continued with more turnovers over time. The last reaction, 0.001 M DMAP showed a slightly decelerated reaction in comparison to 0.002 M, however, as it was a lesser concentration, it can be said that after four hours there was still less product than the standard concentration. It is important to consider that having good amount of product at the end of the reaction is important for industrial or pharmaceutical areas, etc., and features such as a faster catalyst is to be taken into consideration for production times. Lastly, 0.002 M and 0.001 M reactions slow over time, signifying a point where catalyst deactivation or product inhibition took place.

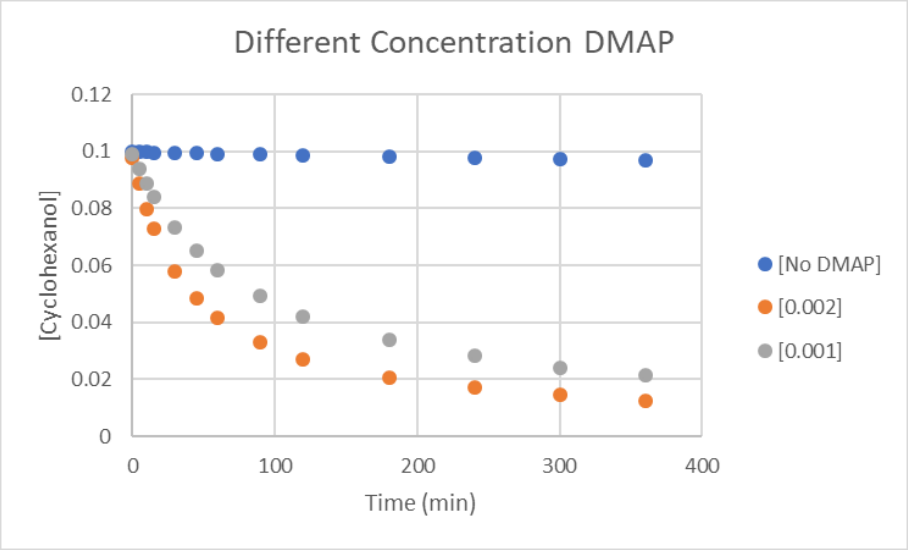

Figure 20. . Different concentration DMAP: No DMAP, 0.002 M & 0.001 M with the standard condition reaction.

CHAPTER IV

CONCLUSION

The present study of the DMAP-catalyzed acylation of cyclohexanol with acetic anhydride in presence of the auxiliary base triethylamine was studied by using the Gas Chromatography (GC) and the Reaction Progress Kinetic Analysis (RPKA). The experimental studies allowed the understanding of the mechanism in a deeper perspective by the reaction rate law with minimal mathematical expertise on the part of the scientist. With gas chromatography, getting the chromatogram of the data provided a rapid and quantitatively information of the reaction behavior, offering general insights useful for further studies. The reaction progress kinetic analysis provided a balance between the information desired and the study of the reaction, as well as the quantitatively data with the time invested of a scientist with fewer experiments by following two protocols.

With all these tools, the understanding of these reactions was simpler by following the RPKA protocols. The study of the different excess of cyclohexanol illustrated a faster reaction by cutting the alcohol concentration in half. Different excess of acetic anhydride showed that a larger concentration can make the reaction faster. Another useful insight was the understanding of the auxiliary base. The different excess of triethylamine from 0.15 M of the standard concentration and 0.30 M as excess demonstrated that the reaction was zero-order as the curves overlapped in the graphical rate equation. However, further studies with different concentrations of the auxiliary base proved that the triethylamine might not contribute with the whole reaction,

but it seemed that it does something at one point during the beginning of the reaction and then it ceases. The same excess reactions showed that catalyst deactivation or product inhibition are not a feature in these reactions, and as the curves from the graphical rate equation overlay, it could mean the reactions are zero-order as the data is closer to the horizontal line.

These findings showed an easier pathway to the study of organic reactions, and by using the gas chromatography and reaction progress kinetic analysis, it was developed an atom-economically method that involves simple manipulation on a graphical approach. Despite a number of precedents, new efficient methodologies for acylation are still on demand.

REFERENCES

1. "Reaction Mechanisms (Article) | Kinetics." *Khan Academy*, Khan Academy, www.khanacademy.org/science/chemistry/chem-kinetics/arrhenius-equation/a/reaction-mechanisms.

2. "6.8 Mechanisms and Arrow Pushing." *Organic Chemistry, 2nd Ed*, by David Klein, John Wiley & Sons, **2015**, pp. 260–263.

3. Moore, Dr. Henry J. "Carboxylic Acids and Esters." *Organic Chemistry Laboratory II*, Pearson Custom Publishing , **2009**, p. 52.

4. Green, W.; Wuts, P. G. M. In *Protective Group in Organic Synthesis,* 3rd ed.; John Wiley & Sons: New York, **1999**; p 150.

5. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis;* Wiley: New York, **1991**.

6. (a) Litivinenko, L. M.; Kirichenko, A. I. *Dokl. Akad. Nauk. SSSR* **1967**, *176*, 97. (b) Steglich, W.; Ho¨fle, G. *Angew. Chem., Int. Ed.* **1969**, *8*, 981. (c) W. Steglich, G. Hçfle, *Angew. Chem.* **1969**, *81*, 1001. (d) Ho¨fle, G.; Steglich, W. *Synthesis* **1972**, 619.

7. Reviews: (a) Ho¨fle, G.; Steglich, W.; Vorbru¨ggen, H. *Angew. Chem., Int. Ed.* **1978**, *17*, 569 ; *Angew. Chem.* **1978**, *90*, 602–615; (b) Scriven, E. F. V. *Chem. Soc. Re*V. **1983**, *12*, 129. (c) Ragnarsson, U.; Grehn, L. *Acc. Chem. Res.* **1998**, *31*, 494. (d) Grondal, C. *Synlett* **2003**, 1568. (e) Spivey, A. C.; Arseniyadis, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5436 ; *Angew. Chem.* **2004**, *116*, 5552 –5557.

8. Tributylphosphine is also known as nucleophilic catalyst for acylation. (a) Vedejs, E.; Diver, S. T. *J. Am. Chem. Soc.* **1993**, *115*, 3358. (b) Vedejs, E.; Bennett, N. S.; Conn, L. M.; Diver, S. T.; Gingras, M.; Lin, S.; Oliver, P. A.; Peterson, M. J. *J. Org. Chem.* **1993**, *58*, 7286.

9. Macrolactonization: (a) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989. (b) Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394.

10. Silylation: Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979**, *20*, 99.

11. Verley, A.; Bo¨lsing, F. *Ber. Dtsch. Chem. Ges*. **1901**, *34*, 3354

12. A. C. Spivey, S. Arseniyadis, *Angew. Chem.* **2004**, *116*, 5552 –5557 ; *Angew. Chem. Int. Ed*. **2004**, *43*, 5436 –5441.

13. Auxiliary Base: (a) Xu, S.; Held, I.; Kempf, B.; Mayr, H.; Steglich, W.; Zipse, H. *Chem. Eur. J.* **2005**, *11*, 4751. (b) S. Xu, I. Held, B.Kempf , H.Mayr, W.Steglich , H.Zipse , *Chem. Eur. J.* **2005**, *11*, 4751 –4757.

14. A. Hassner, in *Encyclopedia of Reagents for Organic Synthesis,* Wiley, Chichester, **1995**, pp. 2022 –2024

15. D. J. Berry, C. V. Digiovanna, S. S. Metrick, R. Murugan, *Arkivoc* **2001**, 201 –226

16. M. R. Heinrich, H. S. Klisa, H. Mayr, W. Steglich, H. Zipse, *Angew. Chem.* **2003**, *115*, 4975 –4977 ; *Angew. Chem. Int. Ed.* **2003**, *42*, 4826 – 4828.

17. A. Hassner, L. R. Krepski, V. Alexanian, *Tetrahedron* **1978**, *34*, 2069 –2076

18. Gas Chromatography Theory, University of California Los Angeles, 1 Apr. **2016**, www.chem.ucla.edu/~bacher/General/30BL/gc/theory.html.

19. “Gas Chromatography (GC).” *Gas Chomatography(GC): SHIMADZU (Shimadzu Corporation)*, 10 July 2019, www.shimadzu.com/an/gc/support/fundamentals/gc.html.

20. Donna G. Blackmond, *Angew. Chem. Int. Ed.* **2005**, 44, 4302 – 4320.

21. Donna G. Blackmond, *Angew. Chem. Int. Ed.* **2005**, 44, 4318.

BIOGRAPHICAL SKETCH

Ms. Tania Veronica Alvarez Castro was born in April 28, 1991 in Matamoros, Tamaulipas, Mexico. She grew up in Matamoros, Tamaulipas where she attended all her basic studies and graduated from high school in 2009. She graduated from The University of Texas Rio Grande Valley in Spring 2017 where she earned her Bachelor of Science degree in Chemistry. She started her master program at The University of Texas Rio Grande Valley in Fall 2017 where she worked as a teaching assistant at the Department of Chemistry during her master's studies. Ms. Tania Veronica Alvarez Castro earned her Master of Science degree in Chemistry in December 2020. She can be reached at taniav.alvarezc@gmail.com.