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Thermodynamic Analysis of PAMAM Dendrimer Synthesis

Ryutaro Einar Jacobson

Andrews University, ryutaro@andrews.edu

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J. N. Andrews Honors Program

Andrews University

HONS 497

Honors Thesis

Thermodynamic Analysis of PAMAM Dendrimer Synthesis

Ryutaro Einar Jacobson

Submitted: April 5, 2021

Advisor: Dr. Ryan T. Hayes

Primary Advisor Signature:

Department: Chemistry and Biochemistry

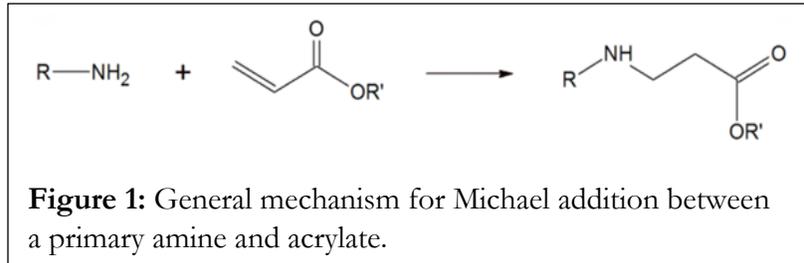
Abstract

The objective of this research was to determine kinetic and thermodynamic data about the reaction between ethylene diamine and methyl acrylate which is used in the production of PAMAM dendrimers. Establishing a rate law and finding values such as rate constant, activation energy, and Arrhenius coefficient will help in determining the best possible conditions for the reaction. A rate law was established through the method of initial rates, comparing the rates of reactions with different initial concentrations to one another. Additional reactions were run with active cooling to observe the effects on rate and reaction progress, and finally reactions were run with varied reactant feed rates in order to test temperature controllability for future optimization work.

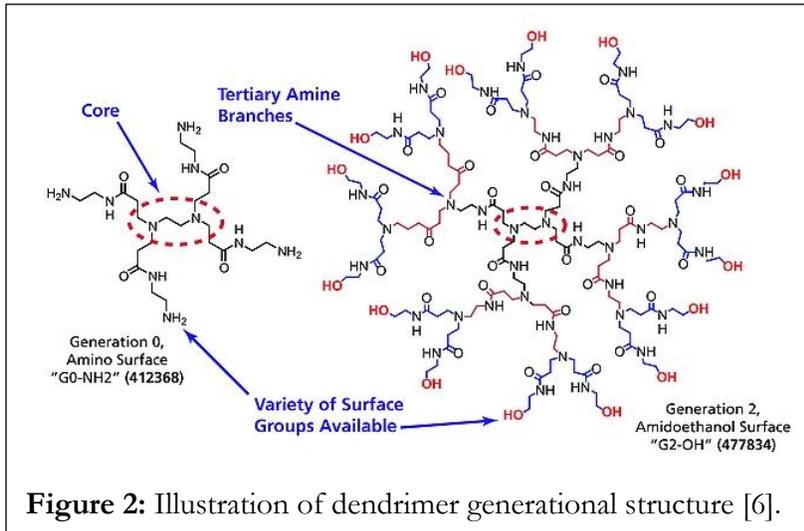
INTRODUCTION

Poly(amidoamine) or PAMAM dendrimers are produced by a sequential, alternating addition of methyl acrylate (MA) to ethylene diamine (EDA). Dendrimers are generally classified by generation, or the number of times EDA and MA have been added to the existing structure. Each reaction is a Michael addition between a primary amine (EDA) and an acrylate (MA), similar to that described by Cheng, et al. [1, 3, 4] The general mechanism for this reaction may be seen in **Figure 1**. Because this addition is the basis of the entire dendrimer structure, a study of this basic reaction is

likely to provide insight into the reaction's behavior in subsequent generations. It is expected that the considerable bulk of later-generation



dendrimers (**Figure 2**) will affect the reaction's performance due to steric hindrance, but the basic mechanism remains the same and later generations of dendrimer are simply too expensive to use on reaction testing. While existing procedures to assemble dendrimers are well documented and functional with acceptable yields, the process tends to be lengthy to the point that some procedures call for a three week reaction period, ensuring that the reaction runs to completion. This long processing time is a result of the heuristic way in which existing procedures have been established,



and is used because it's known to work rather than because of any optimization advantages. In order to optimize a reaction, something must be known about its kinetics and thermodynamics. This is the goal of the present research: to generate data on the basic reaction between ethylene diamine and methyl acrylate in

order to lay the groundwork for optimization. Three primary objectives formed the basis for analysis. Firstly, the reaction's rate law was to be determined using the method of initial rates. Second, the activation energy and Arrhenius pre-exponential factor would be calculated by

comparing reactions under different temperature conditions. Finally, reactant feed control would be implemented in order to test its viability as a means of maintaining ideal reactor conditions. Data was collected using a DS18B20 digital thermometer connected to an Arduino UNO microcontroller [2], allowing temperature data to be written directly to Microsoft Excel. The script and circuit used for this purpose are available in Appendices A and C. The initial stages of the project were spent programming the device and checking for accuracy and reliability. Following this the method of initial rates was used to determine performance based on collected temperature data and serves as the basis for determining rate law [5]. Such an analysis of the dendrimer process' thermodynamics has not been performed, particularly in the context of optimizing existing processes to ideal conditions.

METHODOLOGY

The primary purpose of this research was to determine the rate law of the reaction between ethylene diamine and methyl acrylate. Secondary purposes included determining activation energy, Arrhenius pre-exponential factor, and comparing different system configurations with one another. In order to determine the rate law, the method of initial rates was used [5]. This method requires a known change in concentration of each reactant species one at a time so that each component's effect on the total rate can be measured. Two reactions with different initial concentrations can then be compared using **Equation 1**. Normally rate is expressed in terms of reactant consumed over time, but because instruments which could measure concentration over time, easily interface with computers, and were low-cost were unavailable, temperature was used instead. Because the reaction is exothermic, an increase in the system's temperature is an indicator that the reaction is progressing. The method of initial rates requires two reactions under similar conditions to be compared to one another but only requires initial concentration to be known, so determining reaction rate based on temperature rather than concentration was feasible.

$$\frac{r_1}{r_2} = \frac{k[A]_1^\alpha[B]_1^\beta}{k[A]_2^\alpha[B]_2^\beta} \quad \text{Equation 1}$$

Reaction start time was taken to be the time at which the system temperature began to increase, and the end time was the time when the system temperature began to decrease. Total reaction time was therefore the difference between the two. An example of this may be seen in **Figure 3**. In that example, the beginning would have been taken to be around 355 s, with an endpoint of around 450 s. While the time at maximum temperature wasn't necessarily the true endpoint of the reaction from a concentration standpoint, comparing two reactions

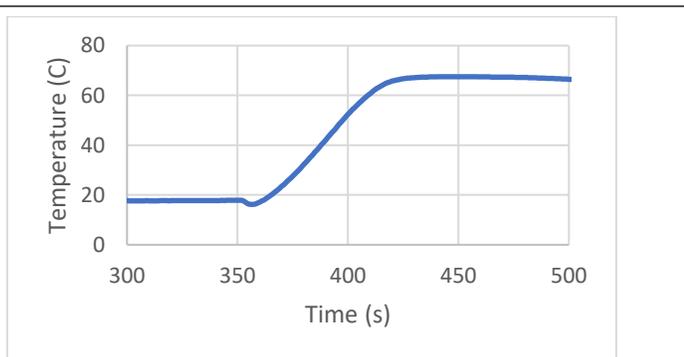


Figure 3: A graph of temperature vs. time for one reaction. Note the start point at around 355 s and endpoint at around 450 s.

with the method of initial rates only requires that a common endpoint be used (mathematically, concentration cancels out of the equation regardless). In order to make results as accurate as possible, three sets of five runs each were performed with no cooling at room temperature (20 °C). In the first set, initial concentrations of both EDA and MA which roughly correspond to those seen in existing procedures were used. These concentrations were 1.60 M in EDA and 6.81 M in MA. In the second set, MA concentration ([MA]) was reduced by fifty percent to 3.41 M, and in the third, EDA concentration ([EDA]) was reduced by fifty percent to 0.80 M. As per recommendations in literature [1], the reactions were run in methanol. In both of the last two sets the species whose concentration was not being changed was left the same as in the first set. In each set, the five runs were conducted with identical starting concentrations and with all other factors (ambient temperature, stirring, etc.) as similar to one another as possible. This was in order to ensure accuracy as the average reaction time across those five runs would be used to determine the reaction's rate with the given initial concentrations. Following this, each of the sets with changed concentration were compared to the original set to determine the order with respect to the changed species. With known rate, concentration, and rate constant k , the exponential orders of the reactions could be determined. This then allowed the precise value of k to be calculated for the temperature at which the reaction was run. With the rate law determined, another set of reactions were performed under the same conditions as the first set except with added cooling. By running the same reaction under a different temperature, it is possible to determine activation energy and Arrhenius pre-exponential factor. These five reactions each began with concentrations of 1.60 M EDA and 6.81 M MA. Ice

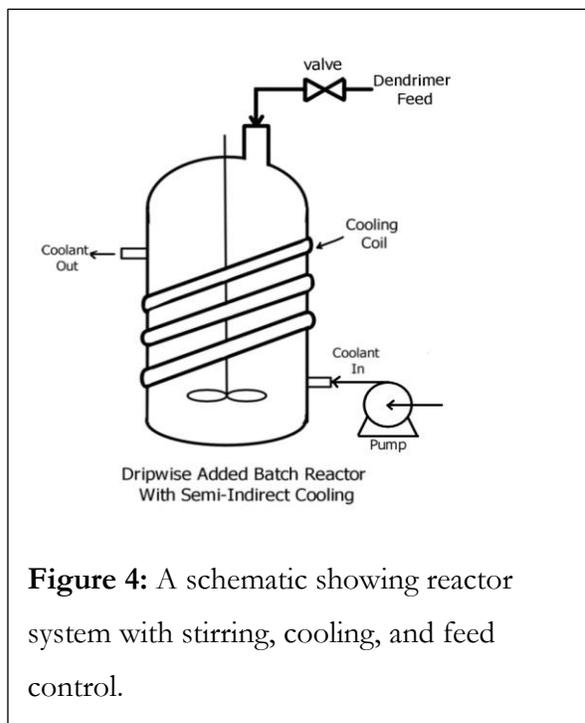
water was pumped through stainless steel cooling coils roughly as shown in **Figure 4** to give a steady internal starting temperature of around 4.5 °C. Once again, the average time for the reaction to run to completion was calculated. Using the Arrhenius relationship shown in **Equation 2**, determining activation energy E_a and pre-exponential factor A is possible.

$$k = Ae^{\frac{-E_a}{RT}} \quad \text{Equation 2}$$

However, one reaction alone is not enough to calculate both A and E_a , so a form of the Arrhenius equation which solves for E_a based on rate constant and temperature was used. This equation may be seen in **Equation 3**. Determining E_a and plugging back into **Equation 2** allowed A to be solved for as well.

$$E_a = \frac{R \ln \frac{k_2}{k_1}}{\frac{1}{T_1} - \frac{1}{T_2}} \quad \text{Equation 3}$$

Finally, a set of reactions were performed to test the effectiveness of reactant feed control in maintaining a target temperature. According to established literature [1] and past experience, the reaction between EDA and MA is best kept at 20-30 °C. As the temperature climbs and especially as it reaches 50-60 °C, the components tend to form polymer chains rather than the desired roughly spherical dendrimer cores. The cooling which had been effected in the previous set was unable to completely absorb heat released by the reaction, indicating that controlling the reaction itself was necessary. To do this, rather than adding EDA directly to the reactor with MA, it was placed in an addition funnel and the stopcock opened such that EDA dripped at regular intervals. The drip rate was measured simply by counting the number of drops which fell over a period of time. Several tests were performed starting with a 130 drop per minute (dpm) rate followed by 35 dpm, 20 dpm, and 22 dpm reactions.



RESULTS

The results of these experiments can be broken up into three sections. The first section is rate law determination with the first three reaction sets, second is calculation of activation energy and pre-exponential factor, and third is testing of reactant feed rate control.

Section 1: Rate Law Determination

Five reactions comprised the first set, but procedural issues in the first two (reactions 1.1 and 1.2) resulted in anomalous data. The volume of reactants used in the first test consumed an unsustainable amount of the limited reactant stocks and nearly filled the reactor. The total amounts of all components were halved from this amount for all future tests in order to prevent supply issues, but reaction scale presented an issue due to mixing difficulties. In this case, reaction 1.1 took 219 s to reach completion compared to the 95 s average reaction time of the last three. This is likely because the doubly large volume prevented the added EDA from efficiently mixing with the MA, therefore slowing the reaction. Reaction 2.2 had a significantly faster apparent reaction time of 82 s, but the initial temperature was 7.81 °C rather than the 16-17 °C initial temperature of the other tests. While precise temperature control was difficult to achieve when the baseline temperature was simply that of the room, fluctuations such as this were abnormal and likely caused by a reactant which had been refrigerated and added while still cold. These initial procedural issues were resolved by the third test of this run, but tests 1.1 and 1.2 were left out of the final calculations due to the aforementioned issues. Reaction time, initial concentration, low temperature, and high temperature for the last three reactions may be seen in **Table 1** below.

	[EDA] (M)	[MA] (M)	Time (s)	Low T (°C)	High T (°C)
Reaction 1.3	1.61 (all same)	6.76 (all same)	106.0	16.37	67.75
Reaction 1.4			99.5	17.50	67
Reaction 1.5			92.5	16.25	67.5
Average			99.3	16.71	67.42
Standard Dev.			6.8	0.69	0.38

Table 1: Initial concentrations, reaction times, and low/high temperatures for the last three reactions of the first set. The first two reactions were left out due to procedural issues.

The second set of tests proceeded in much the same way as the first except with a fifty percent decrease in MA concentration. A change in reaction time here would allow the order with respect to MA to be determined. Because there were no obvious procedural problems with any runs, all were considered in the final calculations. These yielded an average reaction time of 100.5 s, or about a one second increase over the previous set. Reaction order with respect to MA was calculated to be 0.017, or effectively zero. This indicates that MA concentration has no effect on reaction rate and thus is not included in the final rate law. All data for the second set may be seen below in **Table 2**.

	[EDA] (M)	[MA] (M)	Time (s)	Low T (°C)	High T (°C)
Reaction 2.1	1.61 (all same)	3.38 (all same)	134.5	14.81	63.75
Reaction 2.2			115.0	20.00	66.62
Reaction 2.3			88.0	16.87	67.5
Reaction 2.4			88.0	16.87	67.5
Reaction 2.5			77.0	16.06	68.75
Average			100.5	16.92	66.82
Standard Dev.			23.6	1.92	1.88

Table 2: Initial concentrations, reaction times, and high/low temperatures for Set 2.

It is unclear why reactions 2.1 and 2.2 have significantly longer reaction times than 2.3-5 because nothing was changed in procedure or materials throughout this set. There are, however, interesting similarities between the first two and the last three. Both tests 2.1 and 2.2 present gradual changes in temperature throughout, while tests 2.3-2.5 all initially demonstrate a dramatic increase in the rate of temperature change. This is best demonstrated by **Figure 5** and **Figure 6**, which are the derivative graphs of temperature vs. time data for tests 2.1 and

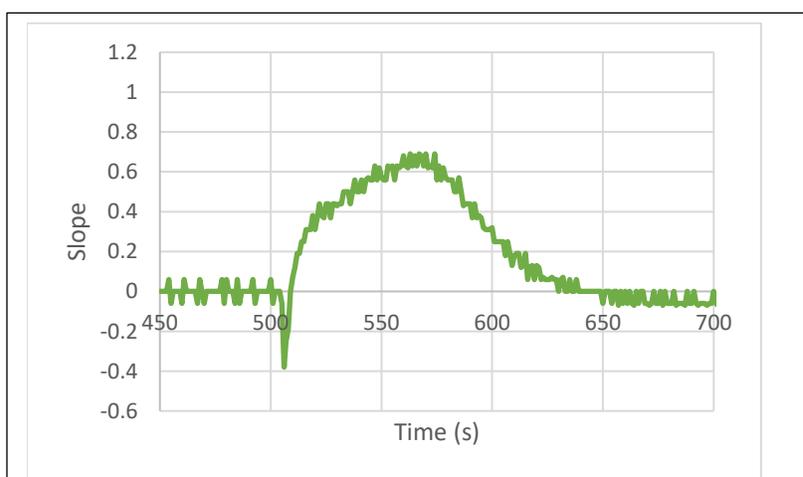
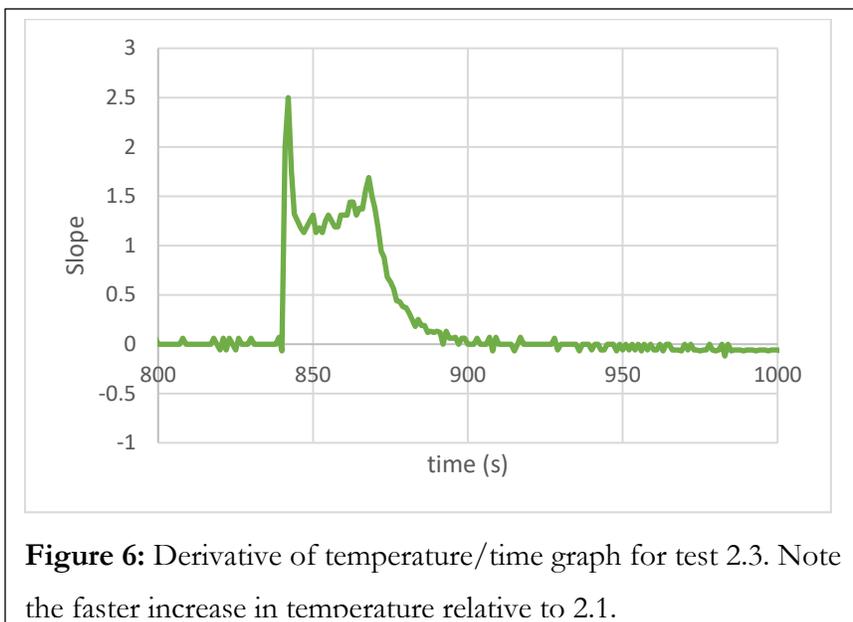


Figure 5: Derivative of temperature/time graph for test 2.1. Note the gradual initial increase in temperature relative to 2.3.

2.3, respectively. Graphs for reactions 2.4 and 2.5 are similar to that of 2.3, while the graph for test 2.2 is similar to that of 2.1.



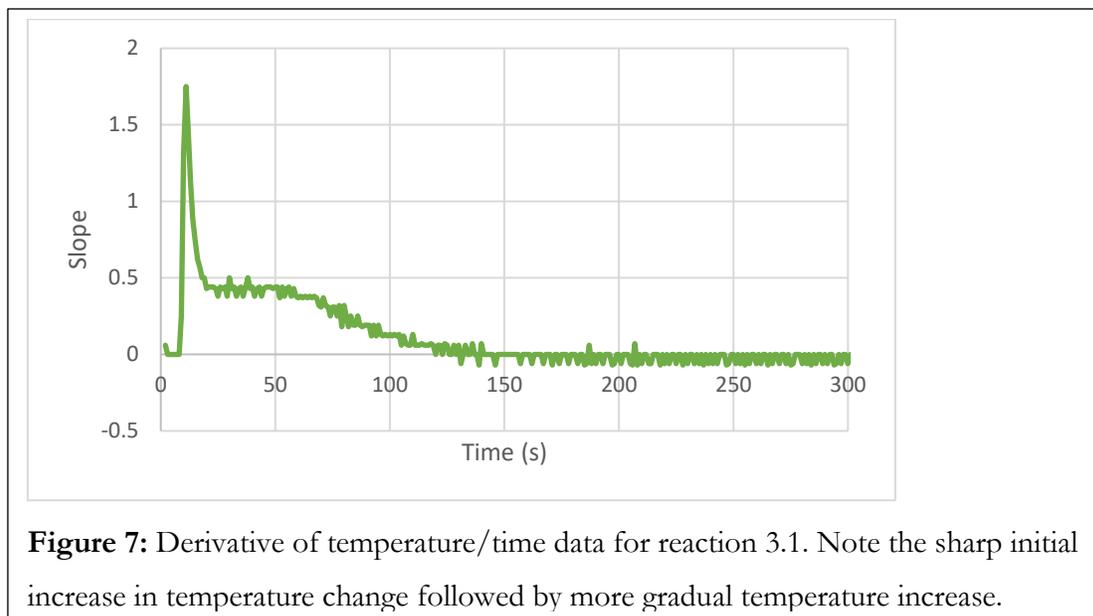
The final set of tests needed to determine the rate law reduced EDA concentration by fifty percent, giving a basis for calculating reaction order with respect to EDA. Taking the average reaction time across all five runs yielded a result of 130.4 s. When compared to the reaction time of set 1, reaction order with respect to EDA was determined to be 0.39. This most closely approximates a $\frac{1}{2}$ order reaction, so this was taken to be the reaction order with respect to EDA. All data used for calculation in Set 3 may be seen below in **Table 3**.

	[EDA] (M)	[MA] (M)	Time (s)	Low T (°C)	High T (°C)
Reaction 3.1	0.80 (all same)	6.76 (all same)	131.5	15.25	54.38
Reaction 3.2			137.5	14.19	52.25
Reaction 3.3			140.5	14.44	51.56
Reaction 3.4			126.5	15.44	52.25
Reaction 3.5			116.0	17.87	55.44
Average			130.4	15.44	53.18
Standard Dev.			9.70	1.46	1.65

Table 3: Initial concentrations, reaction times, and high/low temperatures for Set 3.

Graphs showing the derivative of temperature/time data for Set 3 were similar to those of tests 2.3-2.5. Each one saw a quick initial increase in temperature followed by some settling after a few seconds had passed. An example of this from reaction 3.1 may be seen below in **Figure 7**. This

pattern may be explained by the fact that when EDA is first added, there is nothing but MA in the flask which it may react with. However, as time goes on more product is generated and so less EDA and MA remain to react with each other, resulting in decreased heat generation.



Combining all the results from Sets 1-3, the rate law for the reaction between EDA and MA was determined to be $r = k[\text{EDA}]^{1/2}$. While the zero order with respect to MA was somewhat unexpected, it is entirely possible and the collected data supports this assessment. With the rate law determined, calculating rate constant k was relatively simple. It must be noted that while the rate law applies to the reaction in general, rate constants only apply to the reaction run under a certain temperature condition. In this case, those conditions ranged from around 15-20 °C. k for these temperatures was calculated to be 0.0083 s^{-1} . With rate law and constant determined, reactions could be run at a different temperature to allow for determination of pre-exponential factor A and activation energy E_a .

Section 2: Arrhenius pre-exponential factor and activation energy

In order to determine A and E_a , reactions must be run under different temperature conditions. The reactor flask was immersed in a water bath with stainless steel cooling coils in order to maintain a low temperature for this purpose. With ice water pumped through the coils, the flask's internal temperature stabilized at 4.5 °C. Four reactions were run under these conditions using 1.61 M EDA and 6.76 M MA. EDA was added to MA all at once, as in the first three sets. Data collected for Set 4 may be seen below in **Table 4**.

	Time (s)	Low T (°C)	High T (°C)
Reaction 4.1	59.5	4.69	46.13
Reaction 4.2	61.5	4.56	48.25
Reaction 4.3	66.5	4.56	41.81
Reaction 4.4	55.5	4.06	46.56
Average	60.8	4.47	45.69
Standard Dev.	4.6	0.28	2.74

Table 4: Reaction time, low temperature, and high temperature for Set 4.

Based on this data, rate constant k was determined to be 0.0130 s^{-1} . When rate constants and reaction times were compared between Set 1 and Set 4, data seemed to suggest that the rate of the reaction increased with a decrease in temperature. This in turn indicates a negative activation energy, which is impossible and indicates a limitation of the method used. Reactant concentration is often used to measure reaction progress when attempting to determine rate laws, but no instrument was readily available which could continuously measure concentration as the reaction progressed. As a result, temperature was instead used as an indicator of reaction progress. This method works when comparing reactions under similar temperature conditions, but the active cooling system used in Set 4 appeared to be effective enough that it caused maximum temperature to be reached significantly earlier than in previous sets. Because maximum temperature was being used as the endpoint for calculations, it appeared that lower temperatures were accelerating the reaction, though this was not the case. Accelerated reactions at lower temperatures are considered impossible because activation energy would be negative, which implies there is no energy threshold to overcome when initiating the reaction. As a result, pre-exponential factor and activation energy could not be calculated due to the limitations of available instruments.

Section 3: Testing temperature control through reactant feed rate

The last set of tests were conducted as an initial exploration of temperature control through modifying the rate at which EDA was dripped into the reactor. As with Sets 1 and 4, 11.0 mL of EDA was added to 63.0 mL of MA. In each of the four reactions of this set, a constant drip rate was set and maintained until all EDA had been added. Ideally, the temperature must be maintained under 20-30 °C, which was achieved with a drip rate of around 20 drops per minute (dpm).

Temperature and drip rate data may be seen in **Table 5**. All runs used the same cooling system as in Set 4.

	Drip rate (drops/minute)	High Temperature (°C)
Reaction 5.1	130	35.81
Reaction 5.2	35	34.63
Reaction 5.3	20	24.62
Reaction 5.4	22	22.5

Table 5: Drip rates and high temperatures for feed-controlled reactions.

While tests 5.3 and 5.4 both remained within the 30 °C boundary, they would have crossed it if their respective drip rates had been maintained. These tests do, however, demonstrate the potential of controlling reactant feed to maintain desired temperatures, and the use of a temperature sensor linked to an Arduino microcontroller leaves the possibility of a feedback system which can vary the feed rate for temperature control.

CONCLUSIONS

The progress made during the course of this research may serve as the starting point in a more complete optimization of the basic reaction between ethylene diamine and methyl acrylate. While not introducing new dendrimer varieties or uses, improving dendrimer production analytically rather than heuristically has potential to greatly improve the efficiency of dendrimer research in general as well as production of PAMAM dendrimers in particular. While the current method used to determine the rate law is effective in that capacity, it couldn't be used to determine all kinetic data such as activation energy and Arrhenius pre-exponential factor. The most obvious way to remedy this would be to measure reactant concentrations as the reaction progresses, but with available instruments this has proven difficult (hence the use of temperature sensors rather than concentration monitoring). It is possible that future research could bind optically active molecules to the reactants in order to track concentration through spectroscopy, but appropriate molecules and a way to implement them have not been determined at this time. This limitation makes it difficult to precisely define the ideal conditions for the reaction. On the other hand, use of a temperature sensor has opened potential paths for more efficient processing through automation. The cooling system used is effective in keeping the temperature within desired boundaries, and the fact that an Arduino microcontroller was used to take data from the sensor opens up the possibility of automatically

controlling reactant feed rate. Future research in this direction could establish a feedback system which reads reactor temperature and modifies reactant feed rate in order to keep temperatures within a specified boundary. If this were the case, a researcher could simply input a desired temperature limit and allow the reaction to run. Furthermore, if some automatic correction was implemented such as PID control (proportional-integral-derivative), the system could automatically predict future temperatures based on current temperature data, using it to speed up or slow down reactant feed as necessary. A script which may be used to implement this can be seen in Appendix B. This would allow the fastest addition of reactants without exceeding temperature limits, all without requiring a researcher to spend time monitoring the reaction. As a project primarily concerned with optimization, any next steps will likely move in the direction of process engineering.

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APPENDIX A

```
#include <OneWire.h>
#include <DallasTemperature.h>

#define dataPinPWM 4

//dataPinPWM is the data pin variable, set to 4 because PWM pin 4 will be
used
OneWire oneWire(dataPinPWM);
//Set up oneWire to communicate with any OneWire devices
DallasTemperature sensors(&oneWire);
//Passes the oneWire reference to Dallas Temperature sensor

void setup(void)
{
  Serial.begin(9600);
  sensors.begin();
  //Set baud rate to 9600, initialize sensor
}

void loop(void)
{

  sensors.requestTemperatures();
  Serial.print("temperature(C): ");
  Serial.print(sensors.getTempCByIndex(0));
  Serial.print(" - temperature(F): ");
  Serial.println(sensors.getTempFByIndex(0));
  delay(1000);

}
```

APPENDIX B

```
#include <Servo.h>
#include <OneWire.h>
#include <DallasTemperature.h>

#define dataPinPWM 4
//Temp sensor data pin set to PWM pin 4
OneWire oneWire(dataPinPWM);
DallasTemperature sensors(&oneWire);
Servo valveServo;

void setup()
{
  Serial.begin(9600);
  //Set temp sensor baud rate
  sensors.begin();
  //initiate temp sensors
  valveServo.attach(9);
  //Servo control pin set to PWM pin 9 on Arduino UNO
  valveServo.write(0);
  //Default valve position 0 degrees (closed)
}

int timeDelay = 1000;
//sampling rate = 1 Hz
float targetTemp = 30;
//Temperature controlled to 30 C
float temperature;
float output;

//float sysGainK = 50.71;
//Gain taken as average dT for runs 3-5, set 1, from EDAMARxnNoCoolingData.xlsx,
found in Dendrimer Optimization team files.
```

```

//float tau = 23;

//tau taken as time from start until 63% of K for run 5, set 1 from same place as
sysGainK

float kp = 1;
float ki = 0;
float kd = 0;

float pError;
float iError;
float dError;
float lastError;

float elapsedTime;
unsigned long currentTime;
unsigned long previousTime;

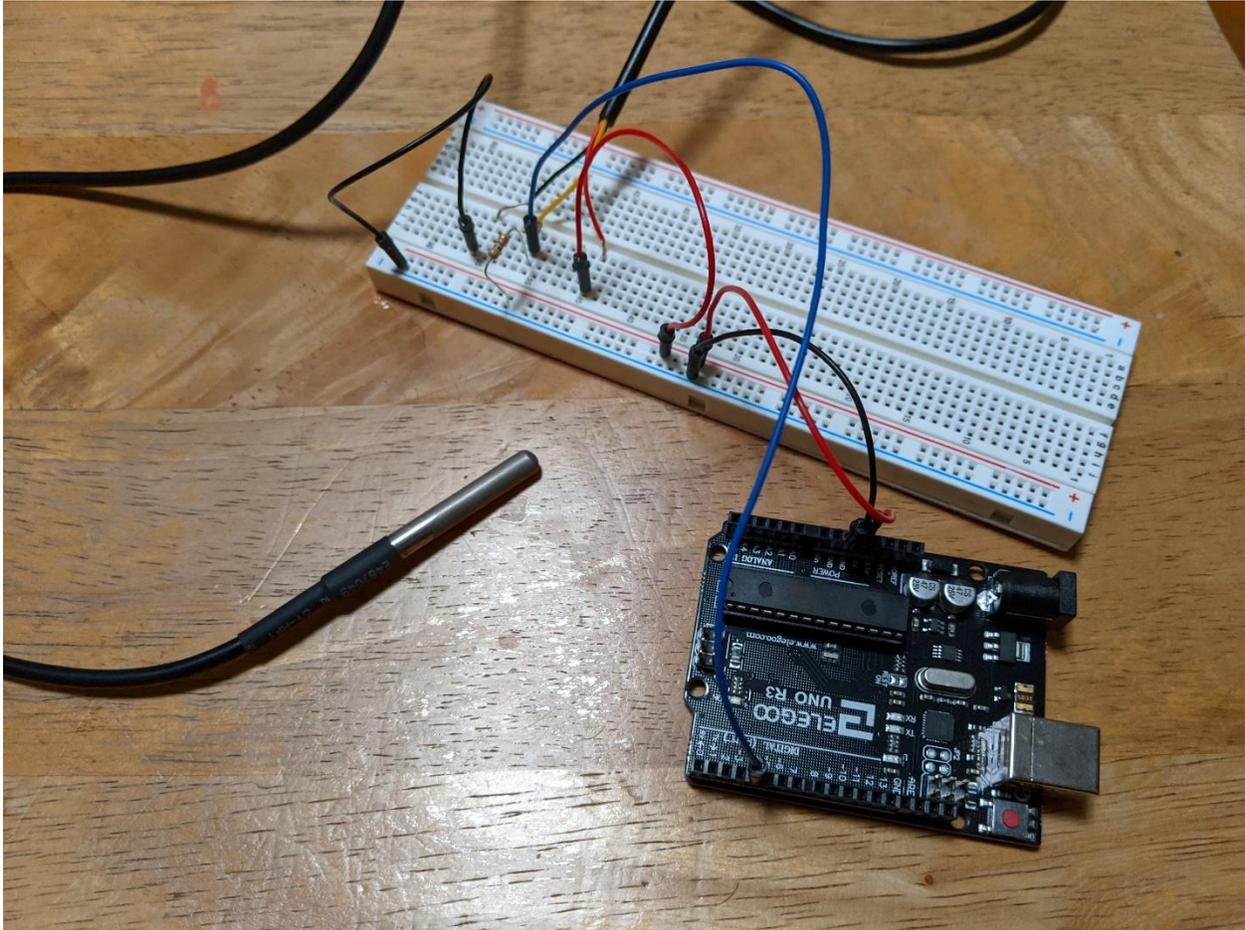
void loop()
{
  sensors.requestTemperatures();
  //Serial.print("temperature (C): ");
  Serial.println(sensors.getTempCByIndex(0));
  temperature = sensors.getTempCByIndex(0);
  output = PID(temperature);
  Serial.println(output);
  delay(timeDelay);
  if (output >= 30)
  {
    valveServo.write(45);
    //sets servo to 45 degrees under specified conditions, will need to be modified
    based on valve used, reaction behavior, etc.
  }
  else if (30 > output && output > 15);
  {
    valveServo.write(20);
  }
}

```

```
    }  
    if (15 > output && output > 5);  
    {  
        valveServo.write(10);  
    }  
    if ( 5 >= output)  
    {  
        valveServo.write(0);  
    }  
}
```

```
float PID(float temp)  
{  
    currentTime = millis();  
    elapsedTime = currentTime - previousTime;  
  
    pError = targetTemp - temp;  
    iError += pError * elapsedTime;  
    dError = (pError - lastError) / elapsedTime;  
    float out = kp * (pError) + ki * (iError) + kd * (dError);  
    lastError = pError;  
    previousTime = currentTime;  
  
    return out;  
}
```

APPENDIX C



The yellow wire coming from temperature sensor is the data wire. This is connected to the blue wire and a $4.7\text{ k}\Omega$ resistor, which limits power through the wire. The blue wire then connects to PWM pin 4. The red and black cables attach to the 5V and GND ports on the microcontroller, respectively. These then connect to the red and black cables of the temperature sensor to provide power.