

API Synthesis in a Batch Reactor: Production of Benzoic Acid as a Model System

Kendall Ankudovich
kenanku@hotmail.com

Kanika Chandra
koala790@aol.com

Rosa Gonzalez
lilballlady44@aol.com

Zachary Martitz
zrm227@yahoo.com

Vincent Mulroe
vmulroe@yahoo.com

Siobhan Powers
spowers89@yahoo.com

Abstract

In this experiment ethyl benzoate was de-esterified in a batch reactor in order to synthesize benzoic acid. The purpose of this experiment was to model the synthesis of API's in a batch reactor. The first and second experiments were tested at 50°C with a 0.35 ethanol mole fraction and the third was tested at 50°C with a 0.25 ethanol mole fraction. The rate constant of the first experiment was measured to be 1.15 L/(mol•min), the second was measured to be 0.686 L/(mol•min), and the last was measured to be 0.876 L/(mol•min). These results provide new information on the esterification rate constant at a high temperature.

Introduction

Active pharmaceutical ingredients (API's) are the most important ingredient of drugs on the market today. They are the essential part in the drugs that make them work efficiently. API's need to be produced in large quantities and in a reasonable amount of time. Most of the time mass production occurs in batch reactors. Batch reactors are jacketed vessels that come in a variety of sizes, and are used to synthesize API's. The

following photograph is an example of a one-liter batch reactor.



Fig. 1 Batch Reactor

API's are produced using processes such as chemical synthesis, fermentation and extraction, or by recovery from natural resources[3]. A successful API does not come out on the market until it has been approved by The Food and Drug Administration and meets their specific criteria[4]. This can take anywhere from 10 to 15 years.

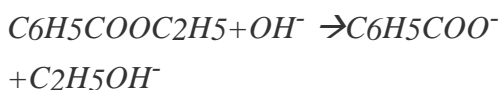
De-esterification and transesterification are processes involved in chemical synthesis. De-esterification is a process in which an ester group is removed from a substance. Transesterification is a process in which ester groups are exchanged between two alcohols. Lipitor was Pfizer's number one selling product of 2006. Atorvastatin is

the API that makes Lipitor function and lowers cholesterol. It can be produced using biocatalytic routes; the final step in producing it is esterification[8].

Making benzoic acid from ethyl benzoate is a model reaction that shows how some API's are made using a batch reactor. Motivation for the study of this second order reaction and its rate constant is that without API's many diseases such as heart disease would be incurable[8]. API's are very important to the human race because they have the potential to save lives, and can be synthesized in a timely manner. Through this educational research project, knowledge of chemical engineering, kinetics, and laboratory procedures can be gained through hands on lab experience.

Background Info/Related Work

In this experiment, we used a de-esterification process to synthesize benzoic acid using ethyl benzoate, ethanol, water and sodium hydroxide. This reaction is depicted below:



Eq. 1

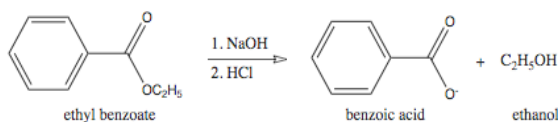


Fig. 2 Chemical Structure

Esterification, de-esterification and transesterification are processes where two compounds, usually an alcohol and an acid, are able to either combine or break apart using ester bonds. These bonds are

important because they provide a way to discover new beneficial compounds that wouldn't be available in the world otherwise. Using de-esterification to synthesize the chemicals resembles many beneficial reactions [1].

Esterification, the combination of two compounds via an ester bond, is used throughout the pharmaceutical field. The Fischer esterification process uses heat to reflux an acid and a primary or secondary alkyl alcohol with a catalyst present, usually sulfuric acid [2]. One example of this is the esterification of acetic acid and ethanol with sulfuric acid as a catalyst forming ethyl acetate with sulfuric acid as a byproduct. One product on the market due to esterification is Lipitor, a drug used for lowering cholesterol. Esterification is becoming an advanced scientific field. With further research, esterification may become a "blockbuster" industry.

Transesterification involves the exchanging of an alkoxy group with an ester group in the presence of another alcohol. It is catalyzed by an addition of an acid or a base. One of the greatest compounds that came from transesterification is biodiesel fuel, which is produced using vegetable oil. Colgate first patented the biodiesel fuel in the 1940's to more readily produce glycerine in order to mass-produce explosives in World War II.

In our experiment, we synthesized benzoic acid, a de-esterification reaction in which an ester bond is removed to produce two byproducts. Although synthesizing benzoic acid wasn't necessarily beneficial in our case, as ethyl benzoate is more expensive than pure benzoic acid [5], it was important in fully understanding how esterification works.

Esterification has become a greatly developed field all around the world.

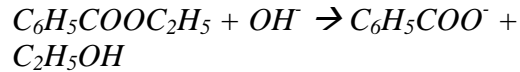
Biodiesel fuel, for example, is being explored not only everywhere in the U.S, but in other countries as well. The U.S. National Renewable Energy Laboratories is one company that continues to research ways to create biodiesel fuel through esterification. Pharmaceutical companies also enjoy working with esterification since they combine two different kinds of compounds. Pfizer and Merck continue to work hard to find drugs that will be able to cure diseases. Pfizer was successful in making the “blockbuster” drug, Lipitor, which made 12 billion dollars to date. Esterification is extremely important in research and also within the food industry.

Benzoic acid is essential in food preservation and creating several chemicals within the pharmaceutical industry. During food preservation benzoic acid is added directly or with sodium, potassium, or calcium salt. Acidic foods such as fruit acid, sparkling drinks, soft drinks, and pickles have benzoic acid within them in such ingredients as vinegar and citric acid. Benzoic acid acts as a pH reducer, which gives a distinct taste within food. Benzoic acid is used to create a large number of chemicals including benzoyl chloride, benzoyl peroxide, benzoate plasticizers, and phenol, which are found in products such as the Whitfield Ointment, used for fungal skin diseases [7].

Experimental/Engineering Design

Motivation

The objective of this experiment is to study the rate of the synthesis of benzoic acid by the reaction



as certain conditions in the experiment are varied. Because ethyl benzoate is not water soluble, ethanol is added to the solution to make the ethyl benzoate ($C_6H_5COOC_2H_5$) dissolve.

Hypothesis

A high mole fraction of ethanol will produce benzoic acid at a lower constant rate, k . Similarly, a low mole fraction of ethanol will synthesize benzoic acid at a high rate.

Procedure

To accomplish this experiment, the following procedures need to be followed:

In a one liter batch reactor, 0.1 N sodium hydroxide (NaOH) is combined with ethanol. The mixture is diluted to 800 mL with water. The batch reactor is set to run at 50° C with the agitator running at 200 rpm. The solution runs in the reactor for forty-five minutes to allow the temperature to reach 50° C. After forty-five minutes, 11.3 mL of 0.1 molar ethyl benzoate is added. This will initiate the reaction.

Immediately following the initiation, a 5 mL sample of solution is taken. Within the sample, the reaction will still be taking place. In order to stop the reaction, the sample is quenched with 5 mL of 0.1 N HCl. The HCl will react with the NaOH within the sample. To determine the concentration of benzoic acid, the sample is titrated with 0.1 N NaOH. The following photograph depicts a titrometer.



Fig. 3 Titrator

The process is repeated in fifteen minute increments. However, it is important to remember that the reaction will proceed at a faster rate at the beginning. Therefore, samples are taken at smaller increments until it is seen that the concentration of benzoic acid is increasing at a slower rate.

Results

Experiments one and two were done under the same conditions. In the batch reactor 0.1 M ethyl benzoate was mixed with 0.1 M NaOH with a 0.35 mole fraction of ethanol. The temperature was set to 50°C. In the third experiment, 0.1 M ethyl benzoate was still mixed with 0.1 M NaOH, however, the mole fraction of ethanol was reduced to 0.25. This experiment was still done at 50°C.

Prior to beginning the experiment, predictions were made as to the outcome of each experiment. For the first and second experiments, we predicted that because 0.1 M ethyl benzoate was used, the concentration of the benzoic acid synthesized could not exceed 0.1 M.

Upon analyzing experiment two, we found our predictions to be accurate. Experiment one, however, was inaccurate due to many sources of possible error and an unfamiliarity with the equipment. For those reasons experiment one was

disregarded. After the titrations of various samples of the batch reactor solution, it is clear that, when 0.1 M ethyl benzoate reacts, benzoic acid cannot exceed 0.1 M. In fact, the concentration of benzoic acid will become asymptotically closer to 0.1 M, but will never actually reach 0.1M. Looking at a graph of the concentration of benzoic acid v. time reveals the relationship.

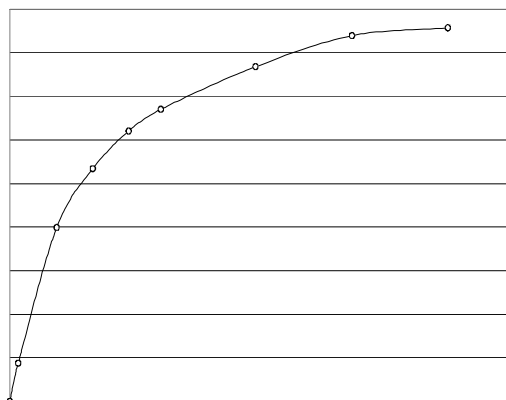


Fig. 4 Concentration of benzoic acid vs. time

In the third experiment the mole fraction of ethanol was decreased from 0.35 to 0.25. It was predicted that because the mole fraction of the solvent was less, the rate of the reaction would increase. Previous literature read aided in the prediction [3].

The analysis of the third experiment had a more rapid rate of reaction than either the first or second experiment. The prediction was consistent with the results. In this experiment, benzoic acid was produced faster than in the other two experiments. Because benzoic acid was produced more rapidly, ethyl benzoate depreciates at a more rapid rate than in the other two experiments. The graph of the concentration of ethyl

benzoate v. time shown below shows the relationship.

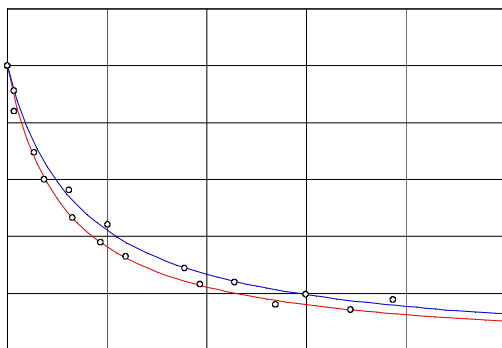


Fig. 5 Concentration of ethyl benzoate vs. time

The red curve represents the third experiment. The blue curve represents experiments number one and two. As evident from the graph, the red curve depreciates faster than the blue curve, demonstrating the effect of ethanol as a solvent. The reason this occurs is because ethanol, in addition to being a solvent, is also a product. By Le Chantilier's Principle, an addition of a product, such as ethanol, will shift the reaction in the reverse direction, slowing down the reaction rate.

The rate constant, k , of each experiment was calculated using the data collected from each experiment. At various times during each of the three trials, samples were taken from the batch reactor and the concentration of benzoic acid was measured via titration. Both the concentration (mol/L) and the time (min) were recorded in Microsoft Excel. The rate constant, k , was calculated using the equation $1/C_A - 1/C_{A0} = kt$.

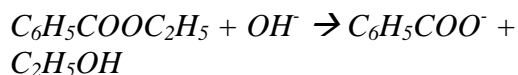
The units of k in this experiment were mol/(L•min). Since k is the reaction rate constant, it was expected that k for the

first two experiments would be nearly the same, and slightly larger for the third experiment, consistent with the curves on the graph pictured above. For experiment two, k was 0.6863 (mol/L•min). It was slightly larger for experiment three at 0.8757 (mol/L•min). These values fit the predictions made prior to the experiment.

Comparing the calculated data from our experiments conducted at 50°C with the theoretical data at 45°C shows how accurate the experiments were. Although the theoretical k 's were conducted at different temperatures than our experiments, comparisons were still made. Taking into account that the theoretical k 's should be slightly less than the calculated k 's due to the lower temperature, our data fits into the range that it should be in.

Conclusions

The pharmaceutical batch reactor laboratory experiment that was performed models API synthesis in the real-world pharmaceutical environment. This method is often used because it can be performed on a large or small scale, depending on a company's needs. Batch reactors are relatively easy to scale, which in turn allows small laboratory production to use simple procedures such as filing, heating, and mixing, or large unit production [3]. In our model of API synthesis, we became familiar with the operation of a computer-controlled batch reactor. We used the reactor to synthesize benzoic acid and ethanol from ethyl benzoate and hydroxide in the de-esterification reaction, shown below:



Ethyl Benzoate + Hydroxide \rightarrow Benzoic Acid + Ethanol

Through knowledge of chemistry and data analysis, our group was able to calculate accurate k values for the experiments we conducted, where k represents the rate constant. The value of k varied, depending on the concentrations of the reactants. The purpose of conducting this experiment was to demonstrate the synthesis of API's in a pharmaceutical setting, and to determine the optimal conditions to obtain an accurate rate constant. For three experiments, three different k values were produced. The third experiment run, being the most accurate, allowed us to determine the most accurate rate constant at 50° C and using 0.25 ethanol mole fraction. This most accurate value of k can be used to determine production of benzoic acid and ethanol on a larger scale.

The results obtained show that the value of the rate constant k increases as the mole fraction of ethanol decreases. In experiments one and two, a 0.35 ethanol mole fraction was used. In experiment three, a 0.25 ethanol mole fraction was used, which gave us a higher k value than the second experiment did. The first trial gave us the highest k value when the ethanol mole fraction was 0.35. This is the only inaccurate data which doesn't follow the pattern of an increase in k as the ethanol mole fraction decreases. This could be because of experimental errors, partially due to the fact that this was the first time we used the equipment, which had not been run for some time. However, when comparing our more accurate results, we observed that the k value increases as the ethanol mole fraction decreases. When this observation is compared to previous experiments recorded in literature, it can be seen that

our results correspond with the following literature:

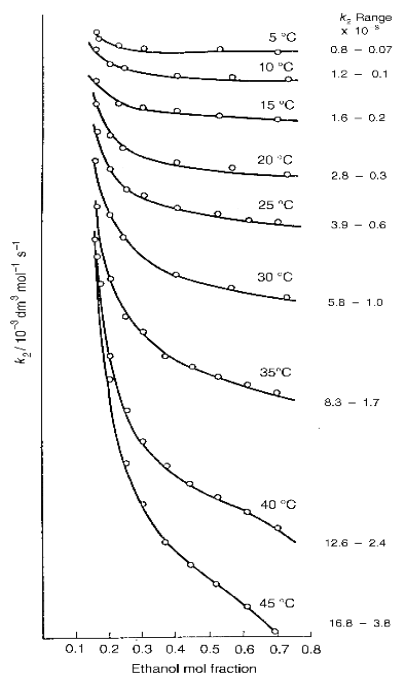


Fig. 6 Literature Data

In the graph above, from a paper by Philip G.N. Moseley and Mustafa Ohag [6], the experiment conducted at the highest temperature was conducted at 45°C. In their experiments, they used the same methods as we did to synthesize benzoic acid and ethanol. They conducted these experiments at different temperatures to observe a trend. They came to the conclusion that no matter what temperature the experiment was conducted at, the k value increased as the ethanol mole fraction decreased. Our research group conducted all three experiments at 50°C. Despite this difference in temperature between our experiments and the experiment conducted in the literature, it is observed in all experiments that the rate constant increases as the ethanol mole fraction

decreases. Therefore, our results corroborate the existing literature.

From the results described in the literature and the results we calculated, it can also be concluded that the specific de-esterification reaction that we conducted is more efficient and more accurate at lower concentrations of ethanol. The de-esterification of ethyl benzoate is a model of the synthesis of active pharmaceutical ingredients in the pharmaceutical industry. Therefore, this experiment can be categorized in the area of biochemistry. This research has helped us learn more about the pharmaceutical and chemical side of engineering. The synthesis of benzoic acid and ethanol not only deals with the production of active pharmaceutical ingredients, but also deals with creating API's more efficiently. This is where chemical engineering plays a role. In recent research, chemical engineers have been attempting to create more accurate and efficient equipment to conduct API synthesis. For example, current research has shown that batch reactors and many other various methods can be created to produce better process control in API synthesis [7]. In addition, our research to find the most accurate rate constant can help in biochemical engineering research to produce faster and cheaper methods of API synthesis. Our experimental model can be used to help determine the most optimal concentrations of reactants needed for the most efficient production of API's.

The synthesis of benzoic acid, an alcohol, is dependant on the amount of ethyl benzoate added to the initial reaction. Over time, more and more benzoic acid begins to emerge. However, not all of the ethyl benzoate will react with the HCl. Approximately ninety

percent of ethyl benzoate is changed into benzoic acid. The other ten percent will likely never to be gathered; it takes an extremely long time for this to react. In business situations, where reactions similar to this are reproduced on a much larger scale, the remaining ten percent is not cared for. If it takes too long to harvest the product, then the company is not making money on the product.

Future Work

There are conditions that could be changed to further solidify the data, but would only be extraneous, considering the accuracy of the results calculated. Temperature and chemical concentration could be easily altered to additionally explore the dependence of the rate constant on these conditions. If the temperature were to be raised from the 50°C used for all the trials, the rate constant would increase. Also, if the chemical concentration of ethyl benzoate were to be increased from the 0.1 M, the rate constant would increase.

The next logical question would be: how would this process work on a larger scale? How could the information found translate to the design of a larger batch reactor? What changes would have to be made so that a kilogram of benzoic acid could be produced? The experimental data could be manipulated to find these figures and conditions. Also, what would the measured rate constants be used for in pharmaceutical production?

In this experiment done in the lab, a one-liter batch reactor was used for 800 ml of ethyl benzoate. 81.9 liters of ethyl benzoate would be needed to produce a kilogram benzoic acid. Therefore, the batch reactor necessary would have to be

able to hold 81.9 liters, so any reactor of a larger volume would be able to produce a kilogram of benzoic acid.

In the lab, within two hours a satisfactory result close to 0.1 M was reached. For this trial, 11.3 ml of ethyl benzoate was used and approximately 9.6 g of benzoic acid was produced. The process of getting a kilogram of benzoic acid using the 81.9 liters ethyl benzoate would take the same amount of time. The reaction time does not change because the properties and concentrations do not change and the ratio between all the reactants and products stays the same.

Measuring the rate constant of the synthesis of benzoic acid is significant for pharmaceutical production because pharmaceutical producers want the greatest efficiency possible. The closer the experimental rate constant is to the ideal rate constant, the more efficient the reaction is. By knowing all the different ways to raise and lower the rate constant, pharmaceutical production can function at the highest performance level achievable.

By measuring all the different variables involved in this reaction, and reactions like this, more efficient equipment can be developed. For example, batch reactors could be further developed with the information from this experiment. The batch reactor could be enhanced in ways to make the process more reliable relative to what scientists expect to happen, and the results that should be produced.

Acknowledgments

We would like to thank the following people for all their support, encouragement, and help throughout our entire research project experience. Firstly, we would like to thank Ms. Jane Oates and the Governor's School Board of Overseers for their support; thank you to the Governor's School administration (Dean Don Brown, Dean Ilene Rosen, and Blase Ur) for giving us this wonderful opportunity to conduct this research at Rutgers University; thank you to our primary project advisor, Professor Henrik Pederson, Rutgers University Chemical & Biochemical Engineering Department Chair, whose guidance in the project is greatly appreciated; and thank you to all the counselors who helped guide us throughout the research process, particularly counselor Sean DiStefano for his patience, guidance, and assistance. Without the help of all the aforementioned people, we would not have been able to conduct or learn from such a valuable and insightful research project.

Works Cited

- 1) ABC Laboratories. API Synthesis / Production under cGMP Conditions.
http://www.abclabs.com/pharma/API_cold.htm
- 2) Fischer Scientific Chemistry Division. Sample MSDS for Benzoic Acid.
<http://www.ilpi.com/msds/benzoic.html>
- 3) Industrial^{IT} Solutions for the Life Sciences Industry. Fully Integrated 21 CFR Part 11 Support Improves Plant Productivity. Active Pharmaceutical Ingredients Manufacturing. 2007.
<http://search.abb.com/library/ABBLibrary.asp?DocumentID=3BUS440003R0001&LanguageCode=en&DocumentPartID=&Action=Launch>.
- 4) INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE. GOOD MANUFACTURING PRACTICE GUIDE FOR ACTIVE PHARMACEUTICAL INGREDIENTS. 19 July 2000.
<http://www.fda.gov/cder/guidance/4011dft.pdf>.
- 5) Jim Clark. Esterification. <http://www.chemguide.co.uk/organicpropos/alkohols/esterification.html>
- 6) Moseley, Philip and Ohag, Mustafa. Thermodynamic functions of activation of the alkaline hydrolysis of ethyl benzoate and of ethyl p-nitrobenzoate in ethanol-water mixtures of various compositions at different temperatures. J. Chem. Soc., Perkin Trans. 2, 1997.
- 7) Paul Giammatteo. Process NMR Applications. <http://www.process-mr.com/process.htm>
- 8) Van Arnum, Patricia. Improving Routes in API Manufacturing. Pharma Ingredients Magazine. July 2007.

