

Biopharmaceutical Production of Benzoic Acid in a Batch Reactor

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Abstract

This experiment investigated the ethanol dependence of the rate constant associated with the synthesis of benzoic acid from ethylbenzoate at 40°C. A batch reactor with 0.25 and 0.3 mole fractions of ethanol was used. The rate constant for the 0.25 mole fraction of ethanol was found to be 0.423 L/(mol•min) and .4027 L/(mol•min) for 0.3 mole fraction of ethanol.

Introduction

Pharmaceuticals and drugs represent a \$550 billion worldwide market [1]. The synthesis of these life-saving compounds is often carried out in batch reactors under tightly controlled conditions of temperature, agitation and chemical composition [2]. In order to rationally develop and design large-scale processes from bench-top experiments, it is important to know how the reaction changes with processing variables. The use of a batch reactor for the evaluation of the second-order rate constant for the synthesis of benzoic acid from ethylbenzoate as a function of the composition of reaction solvent is investigated here. This serves as an example of biopharmaceutical synthesis as practiced in the drug industry.

Background/Information

Benzoic acid is an important chemical ingredient in processed foods. It is used as an antimicrobial additive to a wide variety of foods, among them fruit products, certain baked goods, drinks, condiments, cheeses and frozen dairy. While the compound is well known for its active role in the food industry, its uses cover a significant portion of the industrial and pharmaceutical spectrum. Much of the world's annual benzoic acid output is channeled directly into the production of the translucent crystalline solid phenol, a widely used commercial drug ingredient [3]. Benzoic acid is also converted to caprolactam, a monomer used in the industrial production of nylon fibers [8]. In recent years, the acid has become more prevalent in several chemical processes. These include the adhesive synthesis of plasticizers, the production of alkyd resin coatings, and secondary oil production. The use of benzoic

acid in rubber polymerization, however, has recently declined. In addition to these uses, benzoic acid is utilized medicinally and in cosmetic products. For instance, benzoyl peroxide, a chemical based off of sodium peroxide and benzoic acid, can be used to treat acne.

Many of benzoic acid's pharmaceutical, cosmetic and food uses derive from its antifungal and antimicrobial properties [6]. Also called carboxybenzene or dracylic acid, benzoic acid is an aromatic carboxylic acid with a colorless crystalline appearance and the molecular formula $C_7H_6O_2$. It has a molar mass of 122.12 g/mol. The structural formula of benzoic acid is shown in Fig. 1. [8]

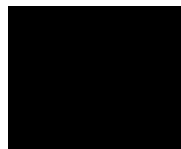


Fig. 1. Benzoic acid structural formula



Because benzoic acid is an essential pharmaceutical ingredient with a high commercial demand, its industrial production must be as efficient as possible. One of the predominant methods of testing and developing chemical processes in the laboratory is the batch reactor technique [2]. Batch reactors are used frequently in the manufacturing of active pharmaceutical products, or APIs, such as benzoic acid [9]. The batch reactor is a chemical reactor in which all reactants are added at once in discrete quantities [2]. As a device that functions both in a compact laboratory form and in a much larger manufacturing size, a batch reactor is ideal for the study of the synthesis of commercial APIs. Batch reactors have high conversion, achieved through extended periods of reactant-in-reactor time. They

function well for the study of how a reaction changes with temperature and reagent concentration because they allow for such precise control of experimental conditions. [2]

How a reaction varies under different conditions is quantified by the rate of reaction. The reaction rate for a given reactant or product is defined as the quantity, in moles or mass units, of the chemical that is either removed or created per unit time, per unit volume. The constant that is specific to a certain reaction's rate equation is uniform regardless of time and is called k . [10]

(eq.1)

The above equation is the standard integrated rate law for bimolecular, or second-order, reactions. K , the rate constant, varies with the concentration of the reagents and with the temperature at which the reaction takes place. The greater the absolute value of k , the more productive the reaction is [12]. The value of k can be found through analysis of data from a series of batch reactor assays. In this experiment, benzoic acid was synthesized from ethylbenzoate, ethanol, and sodium hydroxide in a batch reactor and sampled. The samples were titrated in order to generate a graph of benzoic acid concentration with respect to time.

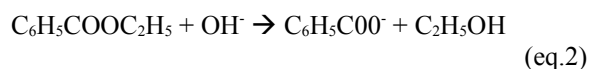


Fig. 2. Autotitrator

Titration, also called volumetric analysis, is a laboratory process designed to determine the concentration of a specific reactant. Using the known information of the titrant (sodium hydroxide) and volume of the analyte, the concentration of the analyte can be determined at the so-called equivalence point. Titration can be done manually with a calibrated burette or, in the case of this experiment, with an automatic titration machine (see Fig. 2). The value of k at different concentrations of ethanol was determined with the aid of graphs generated from the resulting data. [11]

Materials and Methods

In this experiment, Benzoic acid was synthesized from ethylbenzoate as shown in Eq. 2.



Several materials were mixed in the process of producing benzoic acid and ethanol. These were sodium hydroxide, water, ethanol, and ethylbenzoate, all placed in a batch reactor. Next, hydrochloric acid was used to titrate the resulting benzoic acid and ethanol solution, leading to the determination of the reaction rate constant of benzoic acid formation.

In the first reaction, the ethylbenzoate, which is an ester, reacted with hydroxide ions to form benzoic acid and ethanol. The hydroxide ions came from sodium hydroxide, which was added in pellet form. The addition of water ionized the sodium hydroxide, dividing it into sodium, which is a spectator ion, and the hydroxide ion. However, ethylbenzoate is not soluble in water, so another substance had to be added so as to allow for all reagents to dissolve. This substance was ethanol, which allowed both ethylbenzoate and hydroxide ions to be soluble because ethanol is amphipathic, meaning that it contains both polar and non-polar regions.

These first four chemicals, sodium hydroxide, water, ethanol, and ethylbenzoate, were added to a batch reactor, with the ethylbenzoate added last in order to control the starting time of the reaction. The batch reactor helped mix solutions under controlled environments. The batch reactor was interfaced with a Clark controller running on a PC that controlled the temperature and mixing of the solution.

The final stage of this experiment was the titration, which determined the differing molarities of the benzoic acid-ethanol solution at different times, thus allowing for the rate constant to be calculated. At this point, an automatic titrator was used to carry out the titration process mechanically. For this process, hydrochloric acid was added to the benzoic acid-ethanol solution to stop the reaction and placed in a beaker on the autotitrator. The titrator contained a burette holding aqueous sodium hydroxide, which reacted in a neutralization reaction with the benzoic acid that has been placed in the beaker. An electrode was placed in the beaker in order to detect the pH of solution and send the data to a computer. The analysis of this data determines the molarity of the benzoic acid-ethanol solution. [11]

The first step in the preparation for the experiment was to generate the titrant, sodium hydroxide, by setting its molarity. This was done by taking the stock solution and diluting it to the point where it reached 0.1 N. Next the sodium hydroxide was added to the burette of the automatic titrator. The next step of the preparation was to flush pre-existing sodium hydroxide out of the automatic titrator, making sure that only the 0.1 N solution would be used in the titration. In the meantime, the batch reactor was heated up. When the burette was fully cleaned and the batch reactor had reached a constant temperature of 40°C, the experiment began.

Creating the benzoic acid-ethanol solution was the next step in the process. At a constant temperature of 40°C, 495.6 grams of 0.1 M ethanol, 167.7 grams of water, and 3.00 grams of powdered sodium hydroxide were added to the batch reactor. The 11.4 grams of ethylbenzoate were added last to prevent the reaction from beginning prematurely. Assays were taken approximately every five minutes from the reactor. From these samples 5.0 mL were drawn and added to 5.0 mL of 0.1 N hydrochloric acid. Ten samples of differing concentrations were taken and put into an ice container in order to make sure that the reaction had stopped completely.



The second major step in the experiment was the analysis of the benzoic acid-ethanol solution via titration. The first sample of the solution was poured into a beaker and then diluted with water so that the electrode was submerged in the solution. Then, once the machine was turned on,

the titrator began to add sodium hydroxide at intervals and a magnetic stir bar agitated the solution. After the titration was complete, the automatic titrator printed out a page of data that stated the pH of the solution. This titration process was carried out for all ten samples and took about five to ten minutes for each. After each sample was titrated, the experimental portion was complete and only the analysis remained.

The entire experiment was repeated a second time at the same temperature, but at a different concentration of ethanol. The purpose of this replication was to examine the dependence of the rate constant k on the ethanol concentration. This time a 0.3 mole fraction ethanol solution was used, instead of 0.25 mole fraction. 7.5 mL of 10.0 N of sodium hydroxide, 429 mL of 0.3 M ethanol, and 302 mL of

water were added to the batch reactor. Then, to begin the reaction 10.9 mL of ethylbenzoate was added to the batch reactor. The run-through was carried out precisely like the first one in every respect, with the exception of the higher concentration of ethanol. Ten samples were taken at approximately five-minute intervals, and the titration was carried out by the autotitrator.

Results and Discussion

As stated previously, the primary objective of this experiment was to determine how quickly benzoic acid could be synthesized at given reactant concentrations. The rate of reaction is represented by the rate constant “ k ”. The given relationship between the ethyl benzoate concentration (CA), time (t), and the rate constant (k) is given by the differential equation:

(eq.3)

Eq. 3 states that the rate at which the concentration of ethyl benzoate is changing with respect to time is equal to the inverse of the rate constant times the concentration of ethyl benzoate squared. The equation can be arranged to read:

(eq.4)

By taking the integral of both sides, a more pragmatic equation can be found:

(eq.5)

(eq.6)

(eq.1)

This equation can then be used to analyze the collected data.

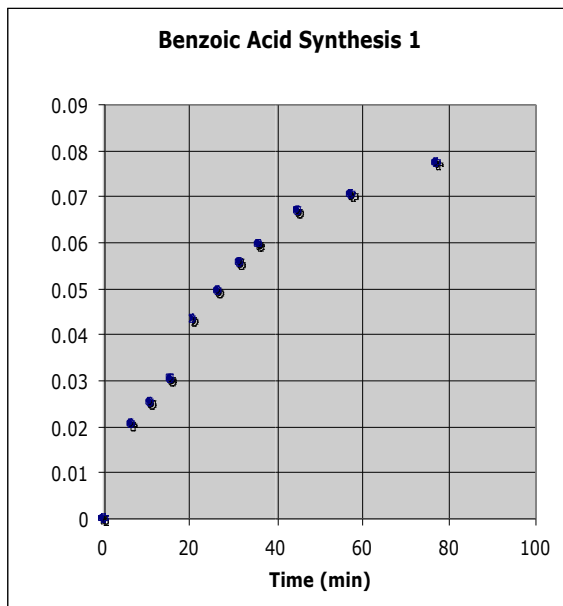


Fig. 3.a. Graph of Synthesis 1

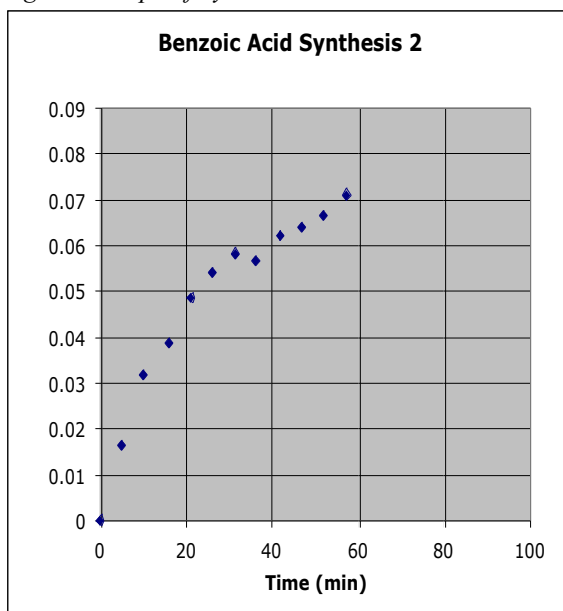


Fig. 3.b. Graph of Synthesis 2

Fig. 3.a and Fig. 3.b. are the benzoic acid concentration (M) vs. time (min) graphs for the first and second runs of the experiment. Both the graphs appear logarithmic because the reaction proceeds rapidly at first but slows down as the concentration of the reactants decreases. Though at first the graph seems to show that more benzoic acid was created with a lower concentration of ethanol than with a higher concentration, this is a false impression. Upon closer inspection, it can be seen that the first reaction ran for approximately 20 minutes longer than the second. When this value is removed, the second

reaction appears to have produced more benzoic acid. Finally, it is important to understand that these graphs can be continued, and that the final concentration of benzoic acid should approach 0.1 N. To test the validity of this prediction, the reactants from the first graph were allowed to remain in the reactor overnight allowing for a substantially extended reaction time. When the sample was titrated, the concentration was, as expected, measured to be extremely close to 0.1 N.

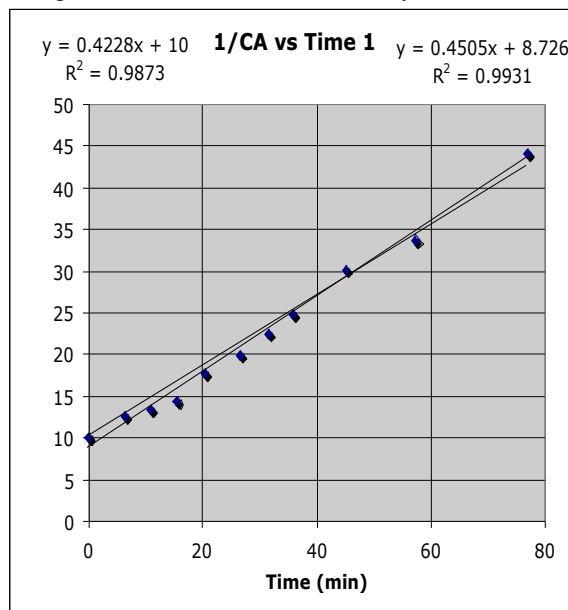


Fig. 4.a. Graph of 1/CA vs. Time 1

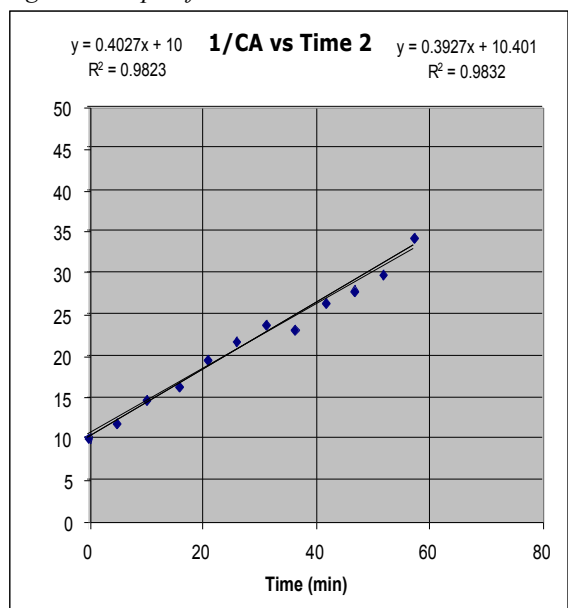


Fig. 4.b. Graph of 1/CA vs. Time 2

By running a line of best fit through the plotted data points of 1/CA over time, it is possible to find the equations of the two graphs (Fig. 4.a and 4.b). The

slope of the linear equation is equal to the rate constant k as can be shown by

(eq.1)

Substituting in 0.1N for t and adding $1/0.1N$ to both sides:

(eq.2)

(eq.3)

The equation takes the linear form of $y = mx + b$. If $1/CA$ is assigned as the y value, t as the x value, and $10 M^{-1}$ as the intercept, it can be seen that k is the slope (m) of the graph. Each of the graphs has two lines of best fit and two respective equations to describe them. The equation on the left is the true line best fit, however, the equation on the right is more accurate because it ensures that at $t = 0$, the CA concentration is 0.1 N ($1/CA = 10$).

The resulting k values of the first and second experiments were .4228 and .4027, respectively. The results concur with pre-existing literature, with the k value decreasing as the mole fraction concentration of ethanol increases. There was not a drastic decrease in the k value because the increase in the mole fraction of ethanol was not great (+ .05 M).

A linear least squares analysis reveals that the line best fit for Fig. 4.b. has a .9935 correlation (r_1) and the line best fit for Fig. 4.a has a .9911 correlation (r_2). Any experiment with data possessing a correlation of .95 or better is considered to be extremely accurate. The variance (R^2) is a measure of the dispersion of a set of data points from the expected value at given points. Both graphs possess high variances of .9871 and .9823 respectively. This means that 98.71% of the points from the first experiment were on the line best fit and 98.23% of the points from the second experiment were on the line best fit. All these point to the conclusion that the analysis of the system was appropriate.

Future Work

There are numerous parts of this experiment that can be further explored. In this experiment, only two very similar mole fractions of ethanol were tested. Further experimentation should be conducted with more extreme variance in ethanol concentration in order to determine whether the trend that as the concentration of ethanol increases, the rate constant decreases, is valid at other ethanol concentrations. If enough concentrations of ethanol were tested, a graph

could be generated to approximate the value of k at any desired concentration of ethanol.

This reaction can also be replicated at different temperatures to observe the relationship between the value of k and changes in temperature. Both reactions discussed here were run at 40°C, but it is expected that the extra energy of a higher temperature would cause the reaction to run faster and thus increase the rate constant.

All the previously proposed experimental variations consist of the modification of the conditions of the reaction. Another possibility is to examine the effect of a different type of reactor on the rate of the benzoic acid synthesis reaction. One modified version of a batch reactor is called a continuously stirred tank reactor, or CSTR. Whereas in a batch reactor all the materials are loaded at one time, in a CSTR the substrate is constantly flowing into the reactor as the resulting solution is removed at an equal rate [13]. There are known disadvantages to continuously stirred tank reactors. One such drawback is a typically smaller product yield, due to the fact that some reactant molecules may pass unchanged through the reactor. However, the reaction rate in a CSTR may be optimized using temperature and concentration manipulation, just as was that in the batch reactor.

Conclusion

The results corresponded with the literature in that when the mole fraction of ethanol was increased, there was a subsequent decrease in the value of the rate constant (k). This means, based on our limited data, that the reaction is more efficient at lower concentrations of ethanol. The results corroborate existing the literature; the statistical analysis of the data for the first and second experiments indicates accuracies of 98.71% and 98.23%, respectively.

This experiment falls in the realm of biochemical engineering, a field that includes research in pharmaceutical drug production. This not only deals with the actual creation of pharmaceuticals, but also how to make these drugs more efficient. In order to earn the most money, a manufacturer would want to create the drug as quickly and cheaply as possible. This experimental model could be used to determine which concentrations of reagents would be most efficient for the production of desired chemicals.

The goal in this experiment was to examine how benzoic acid is isolated for commercial use as well as to analyze the variation of the rate constant at differing concentrations of reagent. First benzoic acid was isolated by means of a batch reactor, and then the

samples were titrated to measure the varying concentrations of benzoic acid. Examination of the data helped to determine the rate constant for the production of benzoic acid at specific concentrations. It was found that the reaction is more efficient (i.e., the production rate of benzoic acid is quicker) at lower concentrations of ethanol.

The Governor's School for Engineering and Technology provided us with an independent research opportunity that, in addition to allowing us to accomplish much in a limited time span, gave us valuable insight into the field of biochemical engineering. In this project we came to understand that the central concept behind this experiment, that is, understanding how reactions change under differing conditions, is widely applicable towards the productive and efficient synthesis of chemicals in the biopharmaceutical field and elsewhere.

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