

Kinetic Study and Intensification of Acetyl Guaiacol Nitration with Nitric Acid–Acetic Acid System in a Microreactor

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Nitration of acetyl guaiacol, one typical aromatic nitration, is highly exothermic and extremely fast. Better control and high efficiency can be achieved in the microreactor due to its enhanced mixing and heat transfer rates. In this study, nitration of acetyl guaiacol was carried out in a microreactor using nitric acid–acetic acid as nitrating agent. The nitration kinetics was first investigated, and a kinetic model was established and revealed good prediction of experimental results at higher temperatures. Effects of molar ratio of nitric acid–acetyl guaiacol, residence time, temperature, and nitric acid concentration on the reaction were studied in detail. Under optimized condition, 90.7% yield of desired product, 5-nitroguaiacol, was achieved with 40% of nitric acid concentration, nitric acid–acetyl guaiacol molar ratio of 2.6, reaction temperature of 120 °C, and residence time of 2 min. Compared to traditional batch reactor, microreactor showed the advantages of higher yield and selectivity, much shorter reaction time, and less use of nitric acid.

Keywords: microreactor, nitration, kinetic, 5-nitroguaiacol

1. Introduction

Nitration of aromatics, a classic and important reaction process, is widely used in the synthesis of many different intermediates including explosives, medicine, pesticides, etc. [1]. Generally, these nitration reactions are extremely fast and highly exothermic, with the reaction enthalpy of most aromatics nitration ranging from –73 to –253 kJ/mol [2]. Therefore, how to achieve efficient mixing, good temperature control, and safety issue are always challenging in traditional batch reactors, which brings plenty of problems, such as pollution, low selectivity, and lack of precise kinetics [3].

The sodium salt of 5-nitroguaiacol is the main ingredient of a new plant growth regulator, which can improve crop quality and yield [4]. 5-Nitroguaiacol is mainly produced via the nitration of acetyl guaiacol as shown in Figure 1. 5-Nitroguaiacol is the desired product with main side product 4-nitroguaiacol due to the steric hindrance effect of –OOCCH₃ group [5–7]. Conventionally, this nitration process is carried out in the batch reactor [5, 6]. The nitrating agent can be various, by employing pure nitric acid, a mixture of nitric acid and acetic acid, and also a mixture of nitric acid and sulfuric acid [8]. A mixture of nitric acid and acetic acid is usually adopted as nitrating agent in this process. Detailed acetyl guaiacol nitration results in batch reactor have been described in previous work. With the residence time of 3 h and the molar ratio of nitric acid to acetyl guaiacol of 4, 63% yield was acquired at 55 °C in a batch reactor, with the residence time of 3 h, the molar ratio of nitric acid to acetyl guaiacol of 4 [5]. Higher yield of 70% was achieved at 90 °C with 1 h residence time in another work [6]. In general, low yield, long residence time, difficult process control, and safety problem are key issues in this process.

In order to improve selectivity, a relatively accurate kinetic model is required for reaction optimization. To get accurate kinetics of nitration reaction is always difficult. Many kinetic studies of nitration of benzene [9], toluene [10], chlorobenzene [11], and nitrobenzene [12] have been described in the literatures. However, most of them are studied in batch reactors, which could hardly ensure isothermal environment and lack accuracy. Microreactor is thought to be a good tool to perform

such fast and exothermic reactions due to enhanced mixing, excellent heat transfer rate, and inherent safety characteristics [13, 14]. On the one hand, microreactor shows better control of the reaction, which is very significant for precise kinetic study [15, 16]. Recently, kinetic model of a fast exothermic Michael addition in microreactors has been reported by Sebastian [17], and it fits with the experimental results well. On the other hand, the fast mixing, better control of temperature, and continuous-flow mode can improve the selectivity to product and decrease the residence time to realize the intensification of nitration process [18, 19]. Over the last decade, a series of nitration of aromatics have been investigated in microreactors such as phenol, salicylic acid, toluene, and benzene [20–23]. The performance is much superior to those in the traditional batch reactors. Yield of nitrophenol increases from 21% to 77% with residence time decreasing from 80 min to 5 min and continuous phenol nitration in a microreactor allows for better control of the exothermic reaction [20]. The reaction rate of toluene nitration in microreactors was found to be 30 times higher than that in the batch reactor by Halder [22].

In this work, a microreactor system was developed to carry out the nitration of acetyl guaiacol in nitric acid–acetic acid. A kinetic model of this reaction was developed to describe the reaction and could fit well with the experimental data. Based on the model, the reaction temperature, residence time, raw material concentration, and molar ratio of nitric acid–acetyl guaiacol were optimized. Compared to the batch reactor, higher reaction rate, selectivity, and less use of fuming nitric acid were achieved.

2. Materials and Methods

2.1. Chemicals. Acetyl guaiacol acetic acid solution (C₉H₉NO₅, 70%) was acquired from Biochemical Science and Technology Ltd. (Zhengzhou). Fuming nitric acid (HNO₃, 95%) and acetic acid (C₂H₄O₂, analytical grade) were purchased from Beijing Beihua Fine Chemicals Co. Ltd.

2.2. Experimental Setup. Figure 2 shows a sketch of experimental setup used for the acetyl guaiacol nitration. It was composed of three pumps, two micromixers, delay loop, a back pressure regulator, and the oil bath. Acetyl guaiacol solution and fuming nitric acid were pumped by two metering pumps

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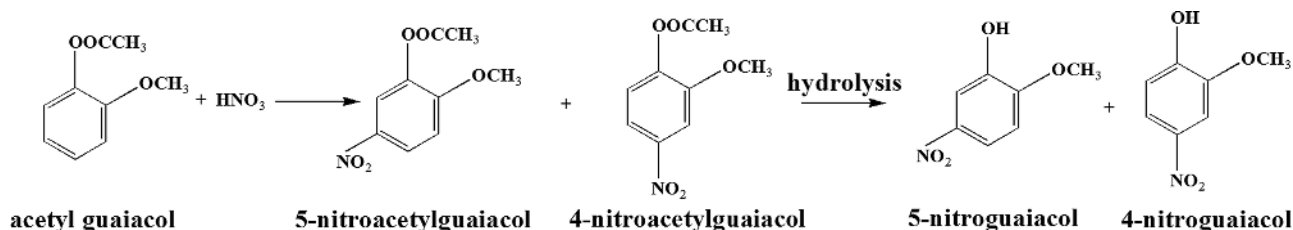


Figure 1. Nitration of acetyl guaiacol

(2PB00C, Beijing Satellite Co.) into the first micromixer (316 stainless steel, inner diameter of 0.25 mm) for mixing, and the feeding temperature was controlled by oil bath (DKU-250A). The mixing performance has been described in literatures [24], indicating that mixing time was within 1 s. After two reactants mixed, they passed through a delay loop (inner diameter of 2 mm) to control the residence time. The range of the delay loop length was from 0.5 to 7 m. The thermocouple (Rex-C700) just before the second micromixer measured the temperature after the reaction. At the same time, excess acetic acid were pumped into the second micromixer to dilute and cool the reaction mixture, quenching the nitration reaction. Back pressure regulator (0–2.5 Mpa) was used to control the system pressure, in case that fuming nitric acid was easy to volatilize at high temperature.

2.3. Analytical Procedure. After the system reached steady state during the experiments, the samples were collected by 20% NaOH solution in order to neutralize excess fuming nitric acid and acetic acid. The mixture was then stirred for 40 min at 90 °C in magnetic stirrer (RCT basic, IKA, 1000 rpm/min) in order to hydrolyze nitro-acetylguaiacol to nitroguaiacol sodium. Lastly, the mixture was acidified with acetic acid. The diluted sample, mainly composed of guaiacol, 5-nitroguaiacol, and 4-nitroguaiacol, was measured by high-performance liquid chromatography (HPLC) (Agilent 1260, Eclipse Plus C18 column, with 3.5 μ m particle size, inner diameter of 4.6 mm, and length of 100 mm) with an ultraviolet detector under the following conditions: flow rate, 0.5 mL/min; detector wavelength, 254 nm; the column temperature, 30 °C; and the mobile phase, methanol (30%) and water (70%). HPLC quantification was performed by using external standard method. The sample volume for all analysis was 20 μ L. The acetyl guaiacol conversion C and selectivity S were calculated by the following equations:

$$C = 1 - \frac{\omega_{\text{gua_sam}} \times F_{\text{tot_in}}}{\omega_{\text{gua_in}} \times F_{\text{gua_in}}} \quad (1)$$

$$S = \frac{\omega_{5\text{-nitro}} \times \frac{F_{\text{tot_in}}}{M_{5\text{-nitro}}}}{C \times F_{\text{gua_in}} \times \frac{\omega_{\text{gua_sam}}}{M_{\text{gua_sam}}}} \quad (2)$$

where $\omega_{\text{gua_sam}}$ (%) is the mass concentration of acetyl guaiacol in the diluted sample, $\omega_{5\text{-nitro}}$ (%) is the mass concentration of 5-nitroguaiacol in the diluted sample, $\omega_{\text{gua_in}}$ (%) is the mass concentration of acetyl guaiacol in the raw material, $F_{\text{tot_in}}$ (g/min) is the mass flow rate of total material, $F_{\text{gua_in}}$ (g/min) is the mass flow rate of acetyl guaiacol, $M_{5\text{-nitro}}$ is the relative molecular mass of 5-nitroguaiacol, and $M_{\text{gua_in}}$ is the relative molecular mass of acetyl guaiacol. Most of the experiments were repeated twice; the average relative errors of replication in selectivity and conversion were both less than 3%, relatively.

3. Results and Discussion

3.1. Kinetic Model of the Reaction. For the kinetic study, the amount of fuming nitric acid was kept at a large excess (nitric acid–acetyl guaiacol >10), so that its concentration could be considered as a constant. In addition, to control the temperature rise, the concentration of acetyl guaiacol was less than 5%, and no obvious temperature rise was observed under this condition. It is a homogeneous reaction. In batch reactor, acetic acid is used for acetyl guaiacol's dissolution [5–7]. The concentration of acetyl guaiacol acetic acid solution used in batch reactor is more than 40%, which is much higher than our raw material.

The plot of conversion of acetyl guaiacol versus residence time at different temperatures is shown in Figure 3. When temperature was as low as 50 °C and 60 °C, conversion was less than 10%. With the increase of temperature, the conversion increased greatly. As it reached 90 °C, complete conversion was achieved within 1 min; in comparison, the conversion was only 70% in

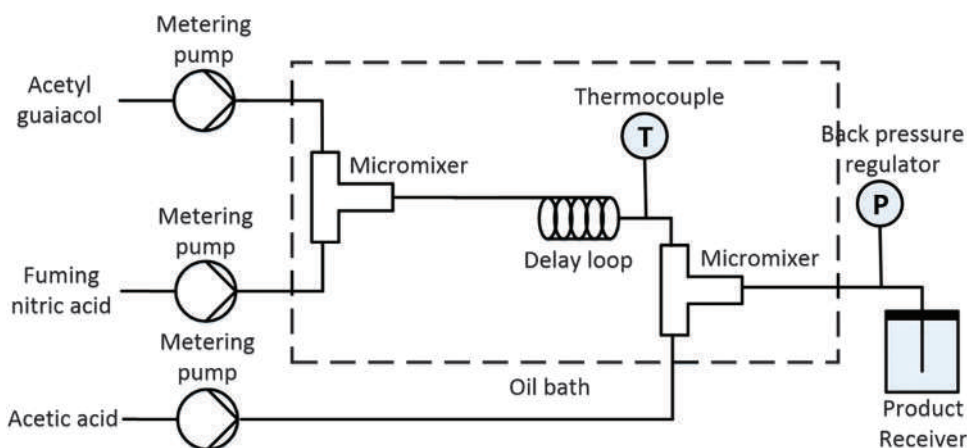


Figure 2. The experimental setup used for the acetyl guaiacol nitration

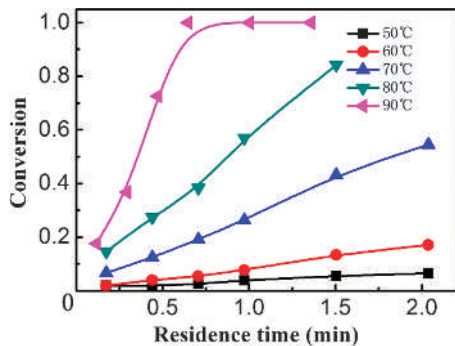
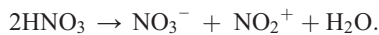


Figure 3. The plot of conversion of acetyl guaiacol versus residence time at different temperatures. Conditions: Molar ratio of fuming nitric acid to acetyl guaiacol, 10, 3% acetyl guaiacol, 7 mL/min; 40% nitric acid diluted by acetic acid, 3 mL/min; system pressure, 0.7 MPa

batch reactor at the same temperature with the residence time of 60 min [6]. The result also revealed that the reaction rate was highly sensitive to temperature. The slope of the conversion–time curve shows that the reaction rate is quickened with the increase of temperature.

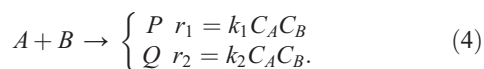
In our experiments, the conditions were well controlled and no other side products were found in the analysis. Thus, it was assumed that only nitration reaction happened during the reaction. For nitration, the nitronium ion of NO_2^+ is proved to be the reactive species in the aromatics nitration and can be acquired in this approach [25]:



The amount of NO_2^+ has a linear relationship with the concentration of fuming nitric acid. According to kinetic model of aromatics nitration in the literature, nitration is first order reaction for both aromatic and nitric acid [22, 26]. Thus, the reaction rate can be expressed as follows:

$$\text{Nitration rate} = k[\text{ArH}] \cdot [\text{HNO}_3]_{\alpha\text{NO}_2^+}. \quad (3)$$

For this parallel reaction, a kinetic model can be established as:



where A represents acetyl guaiacol, B represents fuming nitric acid, P represents 5-nitroacetylguaiacol, and Q represents 4-nitroacetylguaiacol.

As the fuming nitric acid was greatly excess, we could assume that the concentration is constant, viz., $C_B = C_{B0}$. The decreasing rate of acetyl guaiacol could be written as:

$$-\frac{dC_A}{dt} = (k_1 + k_2)C_A C_{B0}. \quad (5)$$

As $C_A = C_{A0}(1 - X)$, the above equation could be changed into:

$$\frac{dX}{dt} = (k_1 + k_2)C_{B0}(1 - X). \quad (6)$$

Taking the integration for the two sides, the equation was changed into:

$$\ln(1 - X) = (k_1 + k_2)C_{B0}t. \quad (7)$$

With linear fitting $\ln(1 - X)$ and t , we can get the value of $k_1 + k_2$.

For the increasing rate of P , $\frac{dC_P}{dt} = k_1 C_A C_{B0}$.

As $C_A = C_{A0}(1 - X)$, $C_P = C_{A0}X S_P$, (S_P represents selectivity of P), the above equation could be changed into:

$$\frac{dX S_P}{dt} = k_1 C_{B0}(1 - X). \quad (8)$$

Taking the integration for the two sides, the equation was changed into:

$$X S_P = k_1 C_{B0} \int_0^t (1 - X) dt. \quad (9)$$

With regressing $\int_0^t (1 - X) dt$ and $X S_P$, we can get the value of k_1 . In the same way, the value of k_2 was obtained.

The conversion of acetyl guaiacol and selectivity to 5-nitroacetylguaiacol and 4-nitroacetylguaiacol were acquired at different temperatures and residence times. $k_1 + k_2$, k_1 , and k_2 could be obtained by fitting the model and the results. The curve fitting for 70 °C is shown in Figure 4. We can see that the model fits the data very well. All the correlation coefficients R^2 are above 0.98.

Calculating kinetic parameters at 50–90 °C and based on Arrhenius equation as $k_i = k_{i0} \exp(-E_i/RT)$, the activation energy and pre-exponential factor could be obtained. The $-\ln k - 1/RT$ curve is shown in Figure 5. It can be concluded that the model fits the data well, with all the correlation coefficients R^2 above 0.98. Kinetics parameters for reactions are listed in Table 1.

As shown in Table 1, activation energy of the whole reaction is the same with 5-nitroacetylguaiacol. This result supports the statement that 5-nitroacetylguaiacol is the main product. Whole activation energy was as high as 139 kJ/mol, which meant that the process is really sensitive to temperature. Besides that, the activation energy of 5-nitroacetylguaiacol generation was obviously higher than that of 4-nitroacetylguaiacol (101 kJ/mol), which meant that the reaction rate to 5-nitroacetylguaiacol is much more sensitive to temperature. Consequently, it could be predicted that increasing temperature may promote 5-nitroacetylguaiacol's generation rate and, accordingly, improve its selectivity and yield.

3.2. Effect of Molar Ratio of Nitric Acid–Acetyl Guaiacol.

Based on the kinetic study, we tried to optimize the conditions to intensify the reaction process. Generally, fuming nitric acid is not greatly excess in industry due to some reasons, such as waste, pollution, and potential side reactions. When fuming nitric acid is not enough, some side reactions such as oxidation and decomposition would increase greatly [2]. Consequently, there always exists an optimal molar ratio of fuming nitric acid to acetyl guaiacol, as it is 4.0 in a batch reactor [7]. Figure 6 shows the conversion of acetylguaiacol and yields to 5-nitroguaiacol at different molar ratios and temperatures in microreactors.

Relatively low concentration of acetyl guaiacol (6%) was chosen to study the effect of various factors due to better temperature control. Twenty percent or even higher concentration of acetyl guaiacol was hard to be conducted in this setup, limited by huge heat released. From the results, as shown in Figure 6, we can find that, when ratio was less than 2.6, conversion and yield increased with the increase of molar ratio; when ratio surpassed 2.6, there was one platform in which yield remained constant with molar ratio increasing. At 110 and 120 °C, complete conversion was achieved once ratio is more than 2.6; therefore, 2.6 could be considered as optimal molar ratio in microreactors. In comparison with batch reactor, the optimal ratio reduced from 4.0 to 2.6, which meant less cost and pollution by nitric acid. This is due to that confined space and process pressure limit nitric acid's volatilization and decomposition in microreactors.

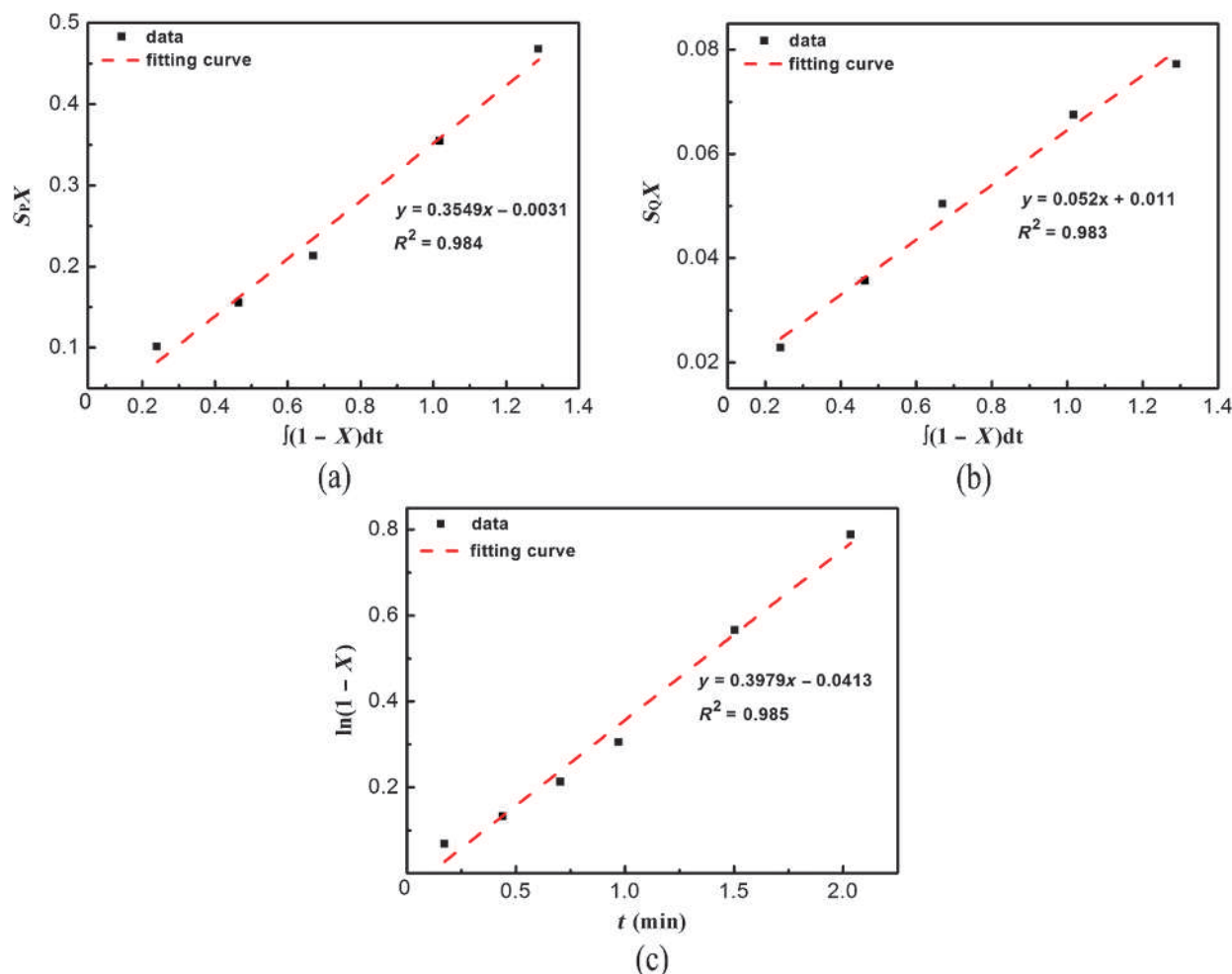


Figure 4. Curve fitting for 70 °C data. (a) k_1 , (b) k_2 , (c) $k_1 + k_2$ (X represents conversion)

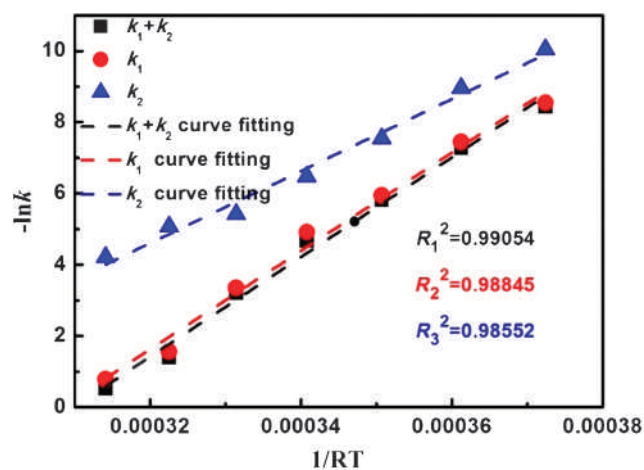


Figure 5. The fitting of $-\ln k$ versus $1/RT$ for kinetic parameters

The pictures of HPLC samples at different molar ratios at 120 °C are shown in Figure 7. When ratio was less than 2.6, the sample color was very deep and precipitation appeared after a period of time. This was due to some byproducts generation from oxidation or decomposition, which could not be quantified with HPLC. [7] With the ratio increased, samples became clear

Table 1. Kinetics parameters for reactions

Reaction	k_{70} ($\text{m}^3/\text{mol s}$)	E_i (kJ/mol)
Whole	6.6×10^{18}	139
5-Nitroacetylguaiacol	2×10^{18}	139
4-Nitroacetylguaiacol	1.15×10^{12}	101

and close to the standard with no precipitation. It can be also concluded that molar ratio of nitric acid to acetyl guaiacol was really important to this reaction and 2.6 was the optimal.

3.3. Effect of Residence Time and Temperature. Effect of temperature and residence time on the selectivity to 5-nitroguaiacol and 4-nitroguaiacol is shown in Figure 8. At relatively low temperature (100 °C), the yield of desired product, 5-nitroguaiacol, increased with the increase of residence time because of no complete conversion. When the temperature was above 100 °C, the conversion was almost 100% and the selectivity (5-nitroguaiacol/4-nitroguaiacol molar ratio) showed little correlation with residence time on these conditions.

With regard to the influence of temperature, the yield had obviously increased with temperature increased from 100 °C to 120 °C. At 130 °C, however, the yield decreased a little bit, probably due to the rise of other kind of side products at extremely high temperature. Particularly, yield of 5-nitroguaiacol reached 90.7% at 120 °C, greatly beyond traditional nitration method in batch reactor. For selectivity, it was also improved with temperature increase, consistent with the kinetic model. The comparison between predicted and experimental values of selectivity at different temperatures is shown in Table 2. The kinetic model revealed fairly good prediction feasibility of experiments at high temperatures.

3.4. Effect of Nitric Acid Concentration in Mix Acid.

Figure 9 shows effect of nitric acid mass concentration in mixed acid in microreactor. From the result, it could be concluded that, with the mass concentration of nitric acid increased from 20% to 40%, conversion increased but, when the concentration was above 40%, the conversion decreased gradually. As stated before, the nitronium ion NO_2^+ was the active substance in

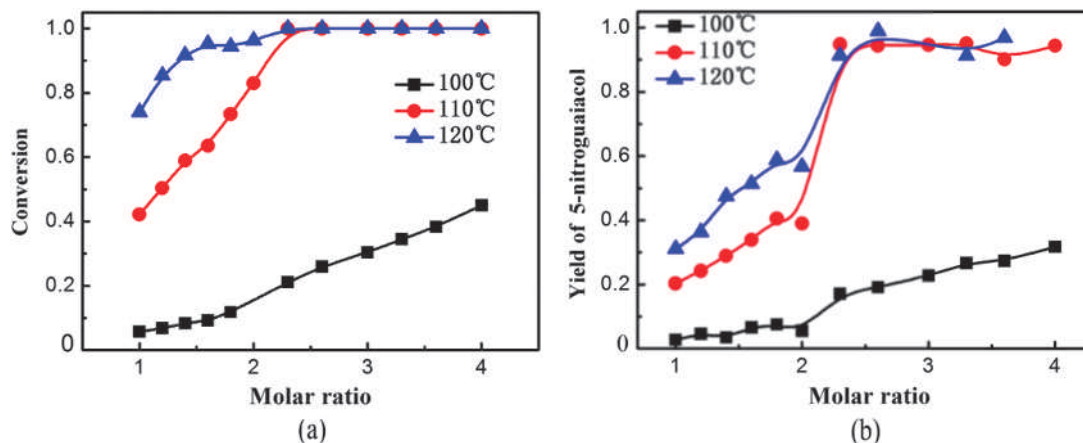


Figure 6. Conversion of acetylguaiacol (a) and yield of 5-nitroguaiacol (b) at different molar ratios and temperatures in microreactors. Conditions: 6% acetyl guaiacol, 6–8 mL/min; 40% nitric acid diluted by acetic acid, 1–2 mL/min; system pressure, 0.7 MPa



Figure 7. Pictures of HPLC samples at different molar ratios at 120 °C. Molar ratios of nitric acid to acetyl guaiacol increase from 1 to 4 in turn

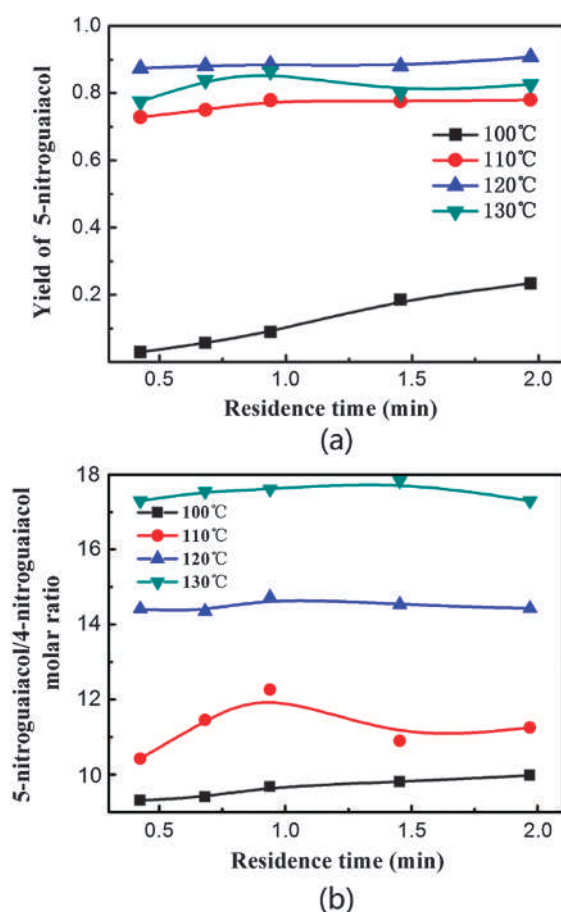


Figure 8. Effect of temperature and residence time. (a) Yield of 5-nitroguaiacol with residence time at different temperatures. (b) 5-Nitroguaiacol/4-nitroguaiacol molar ratio with residence time at different temperatures. Conditions: Molar ratio of fuming nitric acid to acetyl guaiacol, 2.6; 5% acetyl guaiacol, 10 mL/min; 40% nitric acid diluted by acetic acid, 1.3 mL/min; system pressure, 0.7 MPa

Table 2. Predicted and experimental value of selectivity at different temperatures

Temperature/°C	Selectivity	
	Predicted	Experimental
100	8.3	9.6
110	11.4	11.3
120	15.4	14.5
130	20.6	17.5

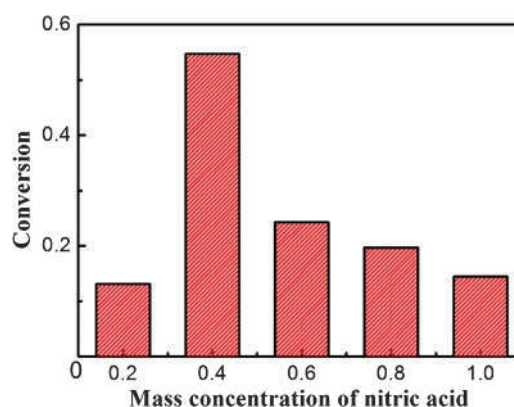


Figure 9. Effect of nitric acid mass concentration in mixed acid. Conditions: Molar ratio of fuming nitric acid to acetyl guaiacol, 2.6; 6% acetyl guaiacol; system pressure, 0.7 MPa; temperature, 110 °C

the nitration, and its generation involved interaction of fuming nitric acid and H^+ from acetic acid. It is simple to explain that NO_2^+ was not enough at low nitric acid concentration. As for the conversion lessening at high concentration, this might be due to the fact that the high concentration nitric acid means low concentration of acetic acid. Therefore, 40% mass concentration of nitric acid was the optimal reaction condition, but more accurate conclusion of nitric acid concentration effect needs to be done in further research.

3.5. Comparison of the Batch Reactor and Microreactor.

A performance comparison between the microreactor and batch reactor is presented in Table 3. 90.7% yield could be achieved in the microreactor with an obviously shorter residence time (2 min) and less use of nitric acid. The result indicates that mixing and transfer rates limited the reaction rate in batch reactor. The deviation of batch results from flow process could be indicated by yield and residence time at similar condition. In batch reactor, yield reached 50% in 60 min at 90 °C; in microreactor, yield reached 82% in 2 min at 110 °C with both nitrate/acetyl guaiacol molar ratio of 4. Considering the temperature difference, the reaction rate will increase by 15 times according

Table 3. Comparison of the microreactor and batch reactor

Reactor type	Molar ratio of nitric acid–acetyl guaiacol	Temperature °C	Residence time/min	Yield/%	STC/(mol/m ³ /h)
Microreactor	2.6	120	2	90.7	1.51×10^4
Batch reactor [6]	4	90	60	70	2.8×10^2

to activation energy. Microreactor still shows high selectivity and efficiency. The much faster reaction rate at high temperature was due to high activation energy of nitration; furthermore, the mass transfer rate was high enough in the microreactor unlike the influence of mass transfer becoming more predominant at higher temperature in batch reactor. Besides that, limited by nitric acid pollution and safety, it was difficult to carry out aromatics nitration at high temperature in a batch reactor, and selectivity of 5-nitroguaiacol cannot be improved. Another important evaluation indicator for two reactors, space time conversion (STC), is compared in Table 3. It represents the converted moles to target product per unit time and volume and represents reactor's capacity. It is shown that STC of microreactor was nearly 50 times that of batch reactor. Hence, nitration of acetyl guaiacol carried out in the microreactor could be much more efficient.

4. Conclusion

A microreactor system was developed for the nitration of acetyl guaiacol using nitric acid–acetic acid as nitrating agent. A kinetic model has been developed, and the kinetic parameters for both main and side reactions have been obtained, which could fit well with the experimental results at higher temperature. Effect of molar ratio of nitric acid–acetyl guaiacol, residence time, temperature, and nitric acid concentration in microreactor were optimized. It is concluded that 40% of nitric acid concentration, nitrate/acetyl guaiacol molar ratio of 2.6, reaction temperature of 120 °C, and residence time of 2 min are the optimal reaction conditions, obtaining 90.7% yield of 5-nitroguaiacol. Compared to traditional batch reactor, the microreactor has the advantages of higher yield and selectivity, much shorter reaction time, and less use of nitric acid. In the future, more work would be done on the strategy to perform nitration of high acetyl guaiacol concentration.

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