

Salsabila, Rani; Perdani, Meka Saima; Kitakawa, Naomi Shibasaki; Hermansyah, Heri

## Article

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# Production of methyl caffeate as an intermediate product to produce caffeic acid phenethyl ester by esterification using cation-exchange resin

Rani Salsabila<sup>a</sup>, Meka Saima Perdani<sup>a</sup>, Naomi Shibasaki Kitakawa<sup>b</sup>, Heri Hermansyah<sup>a,\*</sup>

<sup>a</sup> Department of Chemical Engineering, Faculty of Engineering, Universitas Indonesia, Depok, West Java, 16424, Indonesia

<sup>b</sup> Department of Chemical Engineering, Graduate School of Engineering, Tohoku University, Sendai, Japan

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## Abstract

Caffeic acid (CA) could be considered as an important natural anti-oxidant. However, the low solubility and stability of CA in various solvent is limiting the application in industry. It is advantageous to synthesize alkyl ester of caffeic acid based on both their biological function and potential application. One of the caffeic acid derivatives called caffeic acid phenethyl ester (CAPE) is a compound with numerous important biological activities. To synthesize CAPE one of the method used is catalyzed esterification of caffeic acid and phenethyl alcohol using ion exchange resin catalyst. The first step of the process is to perform esterification of caffeic acid and methanol to produce methyl caffeate (MC). MC would then be used to produce CAPE in the presence of phenethyl alcohol. Herein, the reaction condition and kinetic parameters for the synthesis of MC using cation-exchange resin as a catalyst were investigated, and the product was confirmed by high-performance liquid chromatography (HPLC). The highest yield of MC catalyzed by cation-exchange resin attained under the optimum condition as follows: reaction temperature of 60 °C and a reaction time of 4 h. The esterification kinetics of CA and methanol is described by the pseudo-homogeneous first order model. The relationship between temperature and the forward rate constant gives activation energy of 51 kJ/mol. These results indicated that cation-exchange resin possesses high catalytic activity in the synthesis of MC, which is an efficient catalyst suitable for MC production.

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**Keywords:** Caffeic acid; Cation exchange; Methyl caffeate

## 1. Introduction

Caffeic acid (CA) is one of the most widely distributed hydroxycinnamate and phenylpropanoid metabolites in plant tissues and agricultural wastes [1]. Recently, CA, as a natural anti-oxidant, has received increasing attention

\* Corresponding author.

E-mail address: [heri@che.ui.ac.id](mailto:heri@che.ui.ac.id) (H. Hermansyah).

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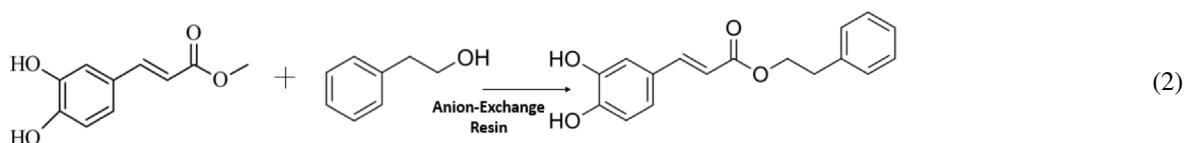
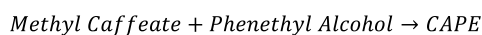
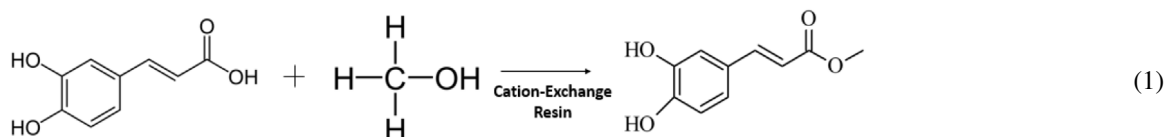
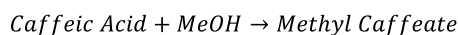
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with regard to its applications in the food, health, cosmetic and pharmaceutical industries because of its numerous biological activities, such as anti-mutagenic, anti-proliferative and anti-oxidant activities [2]. However, CA exhibits low solubility and stability in various solvent systems, thus it is necessary to enhance its practical applicability by improving its solubility. The synthesis of alkyl esters of caffeic acid can significantly improve their biological function and potential application. One of the derivatives of caffeic acid is caffeic acid phenethyl ester (CAPE). Caffeic acid phenethyl ester (CAPE) is a natural phenolic chemical compound. It is the ester of caffeic acid and phenethyl alcohol [3]. CAPE is found in many variety of plants. It is also one of the main medicinal components of the natural product such as propolis which is obtained through extraction from honeybee hives. CAPE is a polyphenol with hydroxyl groups within the catechol ring which is responsible for its crucial role in many biological activities.

There are several existing synthetic methods for CAPE with the main routes of chemical synthesis and biosynthesis. The chemical synthesis methods includes catalytic esterification, reaction of caffeic acid with  $\beta$ -phenyl ethyl bromide, one-pot reaction, malonic acid monoester method and Wittig reaction [4]. Biosynthesis method includes chlorogenic acid hydrolase catalyzed synthesis and lipase catalyzed synthesis [5]. In CAPE production, classical method for the esterification of caffeic acid such as *fischer* esterification, *wittig* reaction and one-pot reaction require tedious operations and generate by-products [6]. Currently, a simple approach of direct catalyzing the esterification of caffeic acid and phenethyl alcohol is being used to synthesize CAPE.

Ion-exchange resin has the potential to be used as substitute for conventional acidic catalytic materials. Ion-exchange resin permit achievement of greater product purity by reducing the side reactions and post reaction of reactants and acids, giving higher yields [7]. Moreover, waste disposal problems are eliminated since no waste acid or base need to be discarded. To produce CAPE using ion exchange resin, the two process involve is esterification of caffeic acid with methanol in the presence of cation-exchange resin to produce methyl caffeate, and the transesterification of methyl caffeate with phenethyl alcohol using anion exchange resin to produce CAPE.

In the production of CAPE, Caffeic acid and methanol alcohol was directly catalyzed for esterification for the synthesis of methyl caffeate (Eq. (1)). The catalyst used in the reaction is cation exchange resin. Then, methyl caffeate and phenethyl alcohol is being directly catalyzed to produce CAPE (Eq. (2)). The catalyst used in the reaction was anion exchange resin.



In this research, direct esterification of caffeic acid in the presence of methanol and cation exchange resin to prepare Methyl Caffeate (MC) will be performed. Besides it, we studied the effect of temperature and ratio between methanol and caffeic acid. In order to study the behavior, we simulated the result to obtain the kinetic parameters. High Performance Liquid Chromatography (HPLC) were used to identify methyl caffeate in the synthesis product.

## 2. Materials and methods

The porous type cation-exchange resin with low crosslinking density, Diaion PK208LH was selected as the most active in the preliminary experiment. The resin was in activated H-form (>99 mol %) swollen with water. The reactant did not easily diffuse into the resin, so that the resin was packed in a column. Methanol was supplied to the top of the column by a metering pump at flow rate of 2.5 cm<sup>3</sup>/min to remove water before the esterification step. The effluent from the column was collected at specific time intervals and the water concentration was determined using Karl Fischer Moisture Titrator and HYDRANAL composite 5 titrating agent.

Decreasing the volume of methanol used for the resin pretreatment is effective in reducing environmental impact and production costs. Therefore, batch esterification was performed using resin pretreated with various volume of methanol. The preheated mixed solution of caffeic acid and methanol and resin were added to glass bottle. The bottle was shaken at 150 rpm in a thermal bath at various temperature. At specific time intervals, the sample solution was collected and the concentration of the reactants were determined using an HPLC system equipped with a UV detector and an ACQUITY HPLC BEH C18 column. The detail of physical properties of ion-exchange resin as shown in Table 1.

**Table 1.** Physical properties of ion-exchange resin.

Diaion	PK208LH
Character	Cation
Type of matrix	Porous
Crosslinking density [%]	4
Particle size [mm]	0.40-0.60
Ion-exchange capacity [mol/dm <sup>3</sup> -resin]	>1.2 × 10 <sup>3</sup>

### 3. Results and discussion

#### 3.1. Analysis of reaction product of Caffeic acid and methanol

Based on the results, CA had been completely converted to MC after the esterification reaction of CA and methanol catalyzed by cation-exchange resin had proceed for 24 h. The high catalytic efficiency of cation-exchange resin was proved via HPLC. The reaction temperature is one of the most important parameter affecting the concentration of MC during the esterification process [8]. Three different temperatures were selected in the range of 40 °C to 60 °C. The MC concentration was increase as well as the increasing of temperature (Fig. 1). Obviously, a higher temperature showed the increasing of reaction rate and equilibrium constant for endothermic reaction.

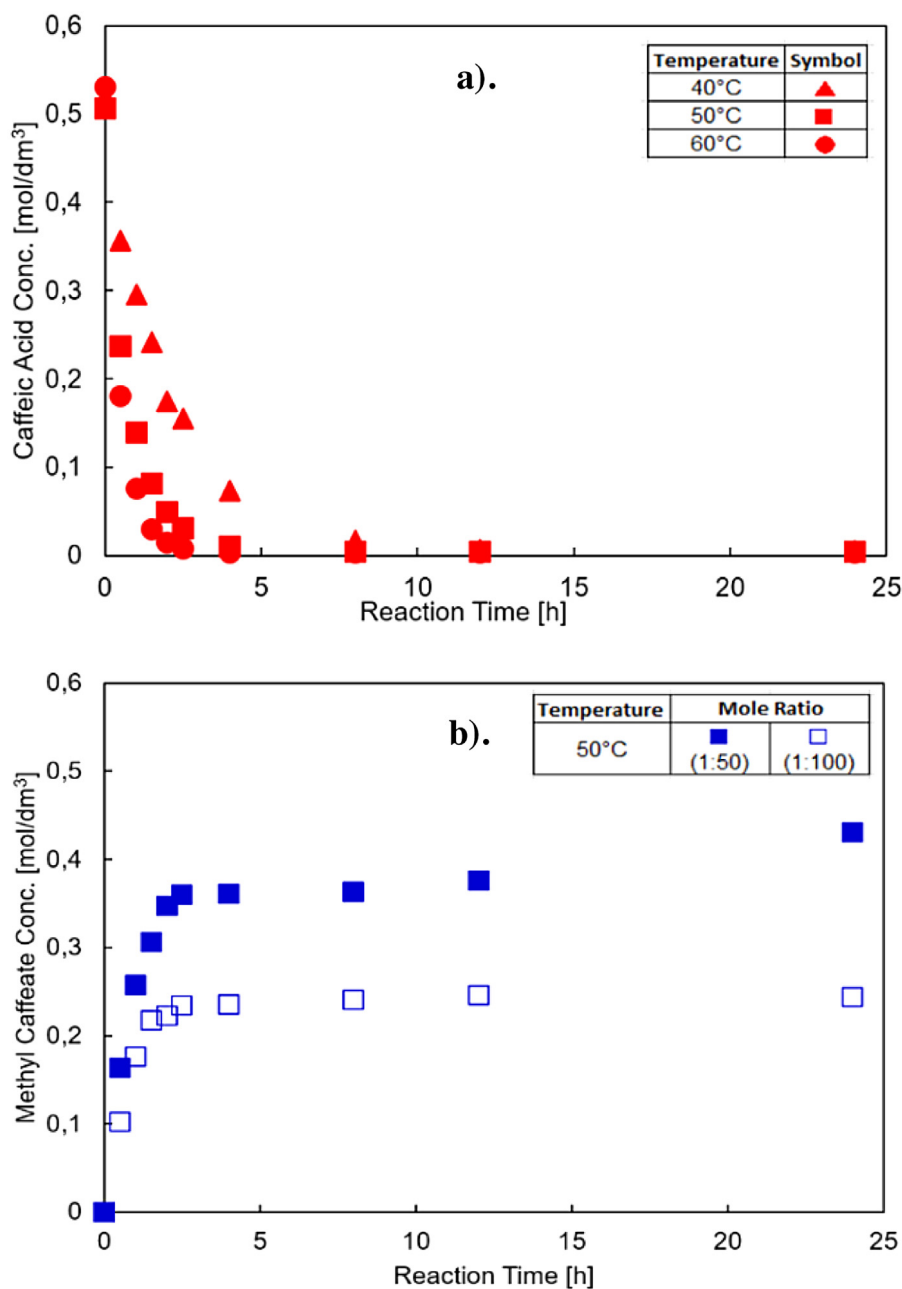
These results indicated that higher temperatures could activate the substrate molecules, reduce the viscosity of the reaction mixture and lead to a higher reaction rate. However, too high of a temperature leads to methanol volatilization. Therefore, a temperature of 60 °C was retained in the subsequent optimization experiment. The time courses of the concentration of caffeic acid and methyl caffeate during the esterification of caffeic acid and methanol are shown in Fig. 1. The highest concentration of methyl caffeate at 24 h can be found when the reaction occurred at 60 °C with the amount of methyl caffeate obtained reached 0.457 mol/dm<sup>3</sup>. The lowest concentration of methyl caffeate at 24 h can be found when the reaction occurred at 40 °C with the amount of methyl caffeate obtained reaches 0.4 mol/dm<sup>3</sup>. The amount of methyl caffeate obtained at 50 °C is 0.431 mol/dm<sup>3</sup>.

#### 3.2. Kinetics of the esterification of CA with methanol in the presence of cation-exchange resin

The effect of the reaction time on the esterification of CA with methanol catalyzed by cation exchange resin at different temperature is shown in Fig. 2. With increasing time, the conversion of CA increased rapidly, which reflects the synthesis ability and stability of MC in the cation-exchange resin catalyzed reaction system. After an esterification time of 2 h for reaction at 50 °C and 60 °C, 8 h for 40 °C, the conversion of CA reached a stable value. Therefore the optimal reaction time was 2 h.

The quantity  $k$  is referred to as either the specific reaction rate or the rate constant. It is almost always dependent on temperature and depends on whether or not a catalyst is present [9]. Kinetic constant can be estimated by plotting  $-\ln\left(\frac{C_A}{C_{A0}}\right)$  which is the concentration of caffeic acid against time. The kinetic constant of the esterification of caffeic acid and methanol at 40 °C is 0.6215, while the kinetic constant of the esterification of caffeic acid and methanol at 50 °C is 1.2585, as for the kinetic constant of the esterification of caffeic acid and methanol at 60 °C is 1.9386. The activation energy ( $E$ ) is a measure of the temperature sensitivity of the rate constant. A high  $E$  corresponds to a rate constant that increases rapidly with temperature. From the Arrhenius equation as shown below:

$$k = A \exp \left[ \frac{-E}{RT} \right] \quad (3)$$



**Fig. 1.** Time courses of caffeic acid (a) and methyl caffeate (b) during batch-wise esterification with cation-exchange resin.

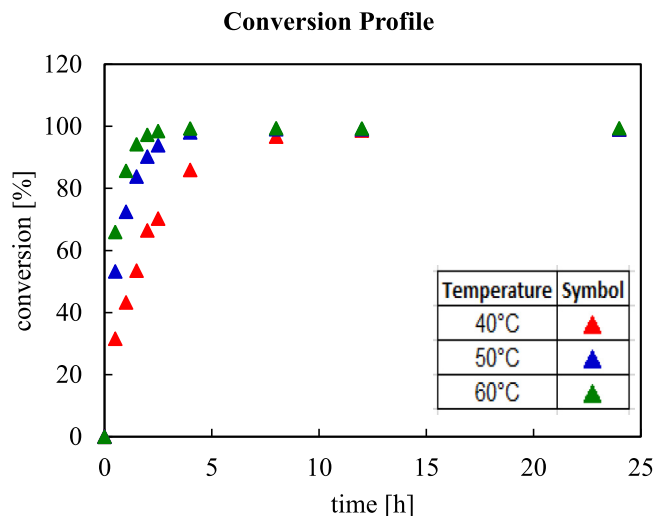
Where  $k$  = rate constant at known temperature

$A$  = pre-exponential factor

$E$  = activation energy

$R$  = gas constant (8.314 J/mol·K)

$T$  = absolute temperature (K = 273.15 + C)



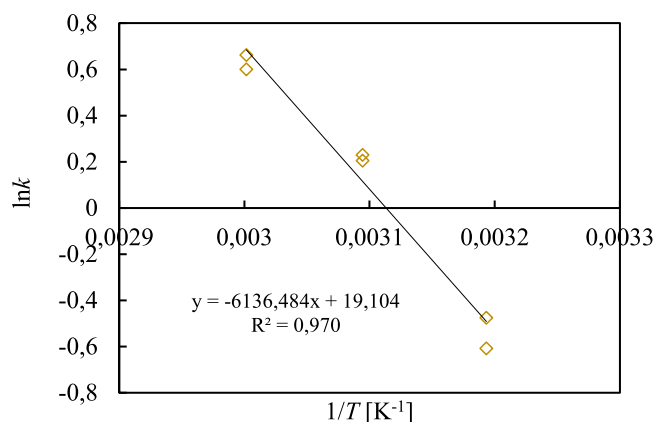
**Fig. 2.** Conversion of caffeic acid at 40 °C, 50 °C, and 60 °C.

In order to determine the activation energy,  $E$ , and the pre-exponential factor,  $A$ , by graphical interpretation, the Arrhenius equation can be written in a non-exponential form. Linearizing Equation above gives

$$\ln(k) = \ln(A) - \frac{E}{RT} \quad (4)$$

By plotting  $\ln k$  against  $1/T$ , the slope equal to  $-E/R$  is obtained and the intercept equal to  $\ln(A)$ . From these known constants, activation energy  $E$  and the pre-exponential factor ( $A$ ) are determined.

As shown in Fig. 3, the exponential term in the Arrhenius equation implies that the rate constant of a reaction increases exponentially when the activation energy decreases. Because the rate of a reaction is directly proportional to the rate constant of a reaction, the rate increases exponentially as well. Because a reaction with a small activation energy does not require much energy to reach the transition state, it should proceed faster than a reaction with a larger activation energy.



**Fig. 3.** Arrhenius plot.

In addition, the Arrhenius equation implies that the rate of an uncatalysed reaction is more affected by temperature than the rate of a catalyzed reaction. This is because the activation energy of an uncatalysed reaction is greater than the activation energy of the corresponding catalyzed reaction. Since the exponential term includes the activation energy as the numerator and the temperature as the denominator, a smaller activation energy will have less of an

impact on the rate constant compared to a larger activation energy. Hence, the rate of an uncatalysed reaction is more affected by temperature changes than a catalyzed reaction. In this experiment, the activation energy is 51 kJ/mol.

#### 4. Conclusions

The reaction conditions and kinetic parameters for the efficient synthesis of MC by esterification of CA by methanol using cation-exchange resin as a catalyst were first investigated. The results indicated that the highest attained yield of CA of 85% was under the optimum conditions *i.e.*, reaction time of 4 h, reaction temperature of 60 °C and mole ratio of methanol to CA of 50:1. A pseudo-homogeneous first order model was demonstrated to justify the experimental data. The model provided good agreement with the experimental kinetic results. The activation energy of the reaction was 51 kJ/mol which indicates that cation-exchange resin possess high catalytic activity in the synthesis of MC.

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