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Kinetics Study Addition Reaction for Methyleugenol with Formic Acid to Produce The Methyleugenol Formic Ester as Intermediate Compound of Hypertension Drug

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ABSTRACT

The methyl eugenol formic ester is the intermediate formation of the 1-(3,4-dimethoxy phenyl)-2-amino-2-cyano propane compound, a hypertension drug. This study aimed to find the value of the reaction order and study the mechanism of an addition reaction of methyl eugenol with formic acid to produce the methyl eugenol formic ester. Gas chromatography analysis of the residual methyl eugenol determines the reaction order. There are two dominant products in the synthesis of methyl eugenol formic ester, resulting in the formation reaction of methyl eugenol formic predictable in a two-way reaction mechanism. The determination of the energy of the reactants, products, and transition compounds in the formation reaction of methyl eugenol formic ester compound prescribed through computational studies using NWChem 6.0 and visualization using Jmol. The results of the analysis of the data obtained several conclusions: The value of the reaction ordered for methyl eugenol with formic acid is the first order. Based on the computational result shows that the enthalpy change for the reaction product is $\Delta H(1) = -47{,}810$ *KJ/mol and* $\Delta H(2) = -60{,}545$ *KJ/mol. The activation energy for both transition compounds is* $Ea(1) = 163{,}1937$ *KJ/mol and* $Ea(2) = 370{,}3477$ *KJ/mol. This fact indicates that the formation of methyl eugenol formic ester compound using the method (1) was more likely than (2). The prediction is based on the determination of Ea with the computational chemistry following the experimental result, which shows the product of (1) more than the product of (2).*

Keywords: methyl eugenol formic ester, reaction mechanism, reaction order, activation energy, and hypertension drug

1. INTRODUCTION

Clove oil is one of the important essential oils. At present, its use is still very limited to several types of products including giving flavor to food products, mouthwash, and chewing gum. Clove oil contains three main components, namely eugenol, eugenol acetate, and caryophyllene. Eugenol compounds are compounds that can be used for various applications such as pharmaceuticals, agriculture, fragrances, cosmetics, and various other industries (Kamatou et al., 2012). Eugenol as the main component can be utilized to produce other compounds, -methyl DOPA from eugenol material through several stages of reaction. The compound 1-(3,4-dimethoxy phenyl)-2-propyl formate is an intermediate compound in the formation of the compound 1-(3,4-dimethoxy phenyl)-2-amino-2-cyano propane which is a hypertension drug. The compound 1-(3,4-dimethoxy phenyl-2-propyl formate is obtained from the addition reaction between polyethylene and formic acid. The interesting thing about the reaction between formic acid and polyethylene is that this reaction is difficult to take place because the two compounds have different polarity properties. As a result, the reaction requires a very large ratio of formic acid to polyethylene and requires high temperatures. Another thing is that the reaction can follow Markovnikov and anti-Markovnikov theories. Major products are products that pass through Markovnikov but at the beginning of the reaction must pass through anti-Markovnikov.

In Klienfelter et al. (1973), the addition reaction of norbornene with formic acid was 98-100 %. Both substances were refluxed for 4 h, forming the compound 2-exo-norbornyl formate. Hole (1994) has charged 0.05 mol of polyethylene with 25 ml of 33% bromic acid in sulfuric acid and dichloromethanes at room temperature, yielding the compound 1(3,4-dimethoxy phenyl)-2- bromo propane in 68% yield. Busroni (1998) initiated the addition of polyethylene with formic acid. The mol ratio of polyethylene to formic acid was 1: 27 and refluxed for 21.5 hours, producing 1-(3,4-dimethoxy phenyl)-2-propyl formate ester with 99.64% purity and 77.8% yield.

The reaction between polyethylene and formic acid produces the compound 1-(3,4-dimethoxy phenyl)-2-propyl formate. The reaction is an addition reaction with carbocation formation following Markovnikov and anti-Markovnikov rules, resulting in two types of transitions and two types of products. In this reaction mechanism study, we will follow the two mechanisms presented in Figure 1.

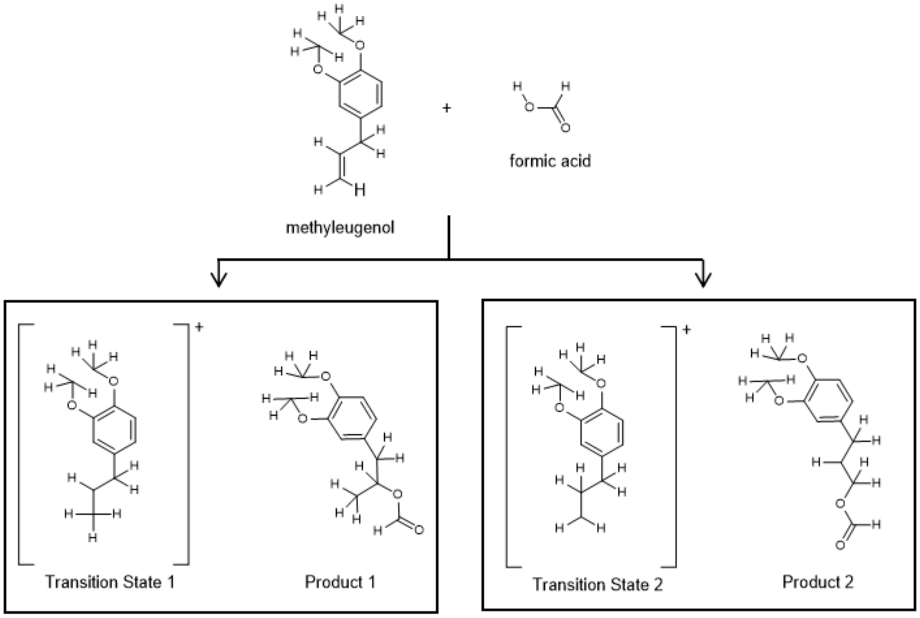


Figure 1. Prediction of reaction mechanism in the reaction of polyethylene with formic acid

Based on the experimental results that have been carried out by several researchers, it is obtained that product 1 has a large yield compared to product 2, so it is estimated that the reaction mechanism is through transition 1. In the research, the study of reaction kinetics in the reaction between formic acid and polyethylene to produce polyethylene formate ester. In studying the kinetics of the reaction, the order of the reaction was determined, and the ratio of the energy of the reactant compound, the energy of the compound in the transition state, and the energy of the product compound. The determination of the reaction order was carried out using experimental methods, while the determination of energy was carried out using chemical computational calculations.

Several previous researchers have researched eugenol and polyethylene compounds. Burkey et al. (2000) studied the cytotoxicity and genotoxicity properties and activation mechanism of methyl eugenol. Gardner et al. (1997) studied the bioactivation of methyleugenol to 1- hydroxy methyl eugenol in Fisher 344 and human liver using cytochrome P450 media. The biosynthesis of estragole and methyl eugenol in Ocimum basilum L. has been studied by Lewinsohn et al. (2000). The essential oil of Croton nepetaefolius which is a medicinal plant containing cineole, methyl eugenol, and terpineol was studied fine nerve mechanical activity has been studied Magalhaes et al. (1998). Sohilait et al. (2003) synthesized secondary alcohol compounds from safrole and polyethylene. Sohilait et al. (2005) synthesized an analog of L-α-methyl-DOPA from eugenol. The biokinetic model of bioactivation and detoxification of alkenyl benzene methylenugenol was studied by Al Subeihi et al. (2010).

Isolation of compounds from Artemisia Japonica sp. Littoricola (Asteraceae) has been successfully carried out by Kwon and Lee (2001). Isolation of active ingredient compounds from clove has been carried out by Zheng et al. (1992) which produced 5 types of active compounds, namely: -caryophyllene, -caryophyllene oxine, -humulene epoxide, and eugenol. The isolated compounds have been used as anti-cancer. Isolation of eugenol compounds derived from Abutilon indicum plants has also been carried out by Ahmed et al. (2002) and the bioactive test of eugenol compound [4-allyl-2-metoxiphenol] isolated showed analgesic activity at doses 10, 30, and 50 mg/kg body weight. Based on the results of research conducted by Purba (2002) stated that the results of distillation with reduced pressure as much as 230 grams with a temperature of 105 - 109 °C at a pressure of 3 mmHg. Eugenol distillation results in the form of a clear yellowish liquid with a specific gravity of 1.068 gram/mL (29 °C). Eugenol isolated from clove oil has high purity, with a retention time of 9,270 minutes. Experimental and theoretical studies have been conducted on the structure and binding energy of eugenol (H2O)n (Longarte et al., 2004).

In the determination of geometry parameters, normal modes of vibrational frequencies, and dipole moments, the results of computational calculations using 3-21G and 3-21G* basis sets on second-row elements have similarities with the results of experimental determination (Pietro et al., 1982). Determination of the energy of compounds in second-row d-orbital effects using 6-31G* is closer to experimental results than energy determination using 3-21G* (Schleyer et al., 1984). The determination of activation energy in cyclobutene and s-trans-butadiene compounds using MP4(SDTQ)/6-31G*// MP2/6-31G* is by experimental determination (Spellmeyer et al., 1987). Geometry optimization results for formaldehyde, ethylene, pyridine, and porphin compounds showed that the calculation results using the 6-31G(d) basis set were in better agreement with the experimental determination results compared to the STO-3G, 6-31G, 6-31+G, and 6-31+G(d) basis sets (Foresman et al., 1991).

2. EXPERIMENTAL

2.1. Chemicals, Equipment and Instrumentation

The required chemical materials include formic acid, sodium bicarbonate, diethyl ether, polyethylene, dichloro methane, potassium cyanide, potassium hydroxide, ammonium chloride, anhydrous magnesium sulfate, 2-propanol, universal litmus. The necessary equipment comprises a reflux apparatus, magnetic stirrer, distillation apparatus, separatory funnel, laboratory glassware, and gas chromatography.

2.2. Research Procedures

20 grams of methyl eugenol was put in a three-neck flask with a capacity of 250 mL, then 98% formic acid was added as much as 110 mL through a separatory funnel in drops at a speed of ± 40 drops/minute while stirring continuously. This mixing process was carried out at room temperature after the addition of formic acid the solution was refluxed using an oil bath with several temperatures of 110 °C and 140 °C with a reflux time of 24 hours. To observe the kinetics every 6 hours the reaction mixture was taken and analyzed by GC. Excess formic acid was distilled, the residue was extracted in a separatory funnel with 10 mL of diethyl ether, and repeated 3 times followed by the addition of 2 M sodium bicarbonate until neutral, tested with universal litmus, then washed with 10 mL of water and then added anhydrous magnesium sulfate, filtered, and evaporated analyzed by GC (Purba, 2002). To determine the reaction order, samples were taken in the range of 6 hours to 24 hours. The mixture obtained was examined using GC.

Computational Devices

Computational research devices used in this research consist of hardware and software. The hardware is a Dual Quad Core computer with 32 GB RAM and 1 TB Hard Disk capacity in the Chemistry laboratory of FMIPA UNIMED. The software used is NWChem 6.0 for calculation, Jmol for visualization of calculation results, and MarvinSketch for drawing 2D structures. The method and basis set used in this research is UHF/6-31G. NWChem 6.0 software was used to perform computational calculations of formic acid, polyethylene, transition compounds 1 and 2, and methyl eugenol formate ester products. The computational calculations performed were: geometry optimization, frequency calculation, energy calculation at ground state, and calculation at the transition state. Jmol is used to create the initial coordinates of the molecular structure and view the output visually.

3. RESULTS AND DISCUSSION

In the laboratory observations, the chromatogram area data of residual methyl eugenol at various times at 110 °C and 140 °C were obtained as shown in Table 1 and Table 2.

Table 1. Chromatogram area of residual methyl eugenol in time variation at 110°C

No	Observation Time (hour)	% Chromatogram area of residual methyl eugenol
1.	5	37,3969
2.	9	6,6246
3.	15	1,9303

Table 2. Chromatogram area of residual methyl eugenol in time variation at 140°C

No	Observation Time (hour)	% Chromatogram area of residual methyl eugenol
1.	6	14,5750

2.	12	5,5396
3.	18	1,0051

Based on the data obtained, the reaction order price can be verified using the first order equation, ln At = ln Ao - kt, which is presented in Table 3 and Table 4.

Table 3. Relationship table between ln(MEu) and t at 110°C

No	Time	MEu	ln(MEu)
1	5	37.3969	3.6216
2	9	6.6246	1.8908
3	15	1.9303	0.6577

Based on the data in Table 5, the curve of the relationship between ln(M Eu) and t at 110°C is shown in Figure 2.

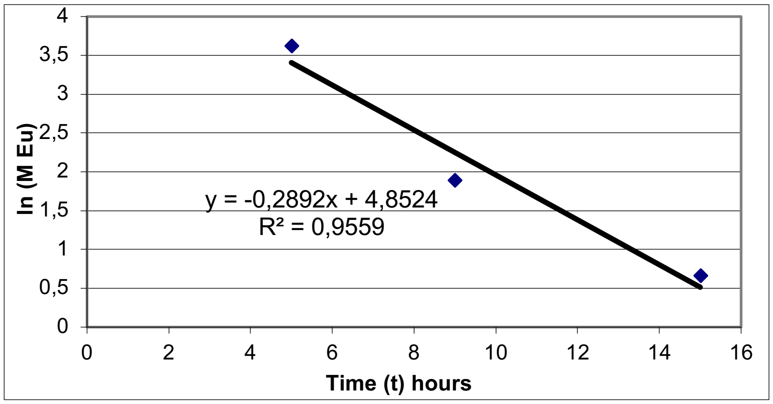


Figure 2. Relationship curve between ln(M Eu) and t at 110°C

Table 4. Relationship table between ln(M Eu) and t at 140°C

No	Time	M Eu	ln (M Eu)
1	6	14.5750	2.6793
2	12	5.5396	1.7119
3	18	1.0051	0.0051

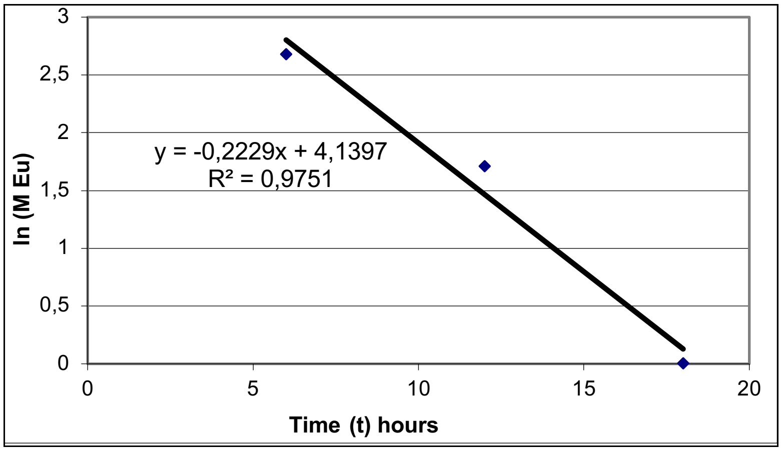


Figure 3. Curve of the relationship between ln(M Eu) and t at 140oC.

To prove that the reaction between methyl eugenol and formic acid is a first-order reaction, it can be determined based on the price of R2. Based on the data in Figure 2 obtained that R2 is 0.955 while the data in Figure 3 obtained that the price of R2 is 0.975. Based on these observations and calculations, it can be determined that the reaction between formic acid and methyl eugenol has a reaction order of 1. This fact has the consequence that the study of the reaction mechanism follows the first-order reaction. One possible mechanism is the formation of carbocations in the addition reaction of formic acid to methyl eugenol. In addition, by using these data, the magnitude of the rate constant (k) can be determined as shown in Table 5.

Table 5 Reaction rate constants at varying temperatures

No	Temperature (°C)	Temperature (K)	k
1	110	383,15	0,2892
2	140	413,15	0,2229

Determination of the reaction mechanism

In the introduction, it was stated that the reaction between methyl eugenol and formic acid (as reactant) to produce methyl eugenol formate ester (as product) is predicted to go through two reaction paths with two transition states and two reaction products. The study of the reaction mechanism is determined using computational calculations through the determination of the amount of reactant energy, transition state energy and the amount of reaction product energy. Based on these data, an energy diagram can be drawn for the reaction of methyl eugenol formate ester formation through two reaction pathways, so that possible reaction mechanisms can be compared based on thermodynamic and kinetic data.

Based on the results of geometry optimization, the energy for the reactant compounds, transition compounds, and reaction compounds is obtained. Figure 4 shows the energy diagram for the addition reaction between methylugenol and formic acid to produce methyl eugenol formate ester.

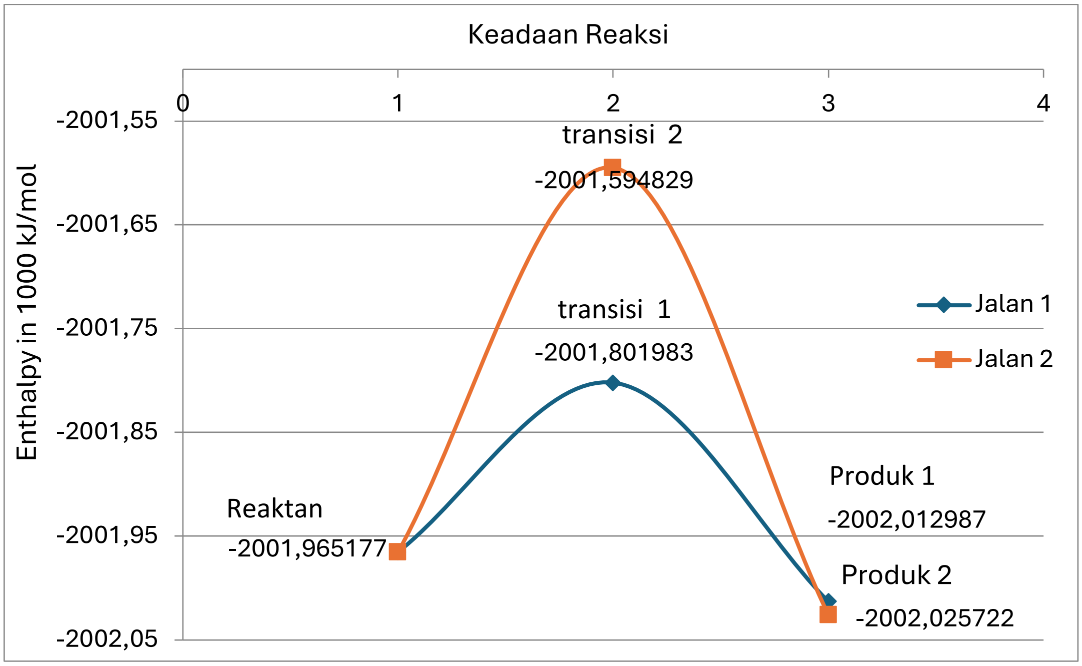


Figure 4. Reaction Energy Diagram of the formation of methyl eugenol formate ester compound

Based on these data, the activation energy of each road can be determined, so the results are obtained: $Ea_{(1)} = 163.1937$ kJ/mol and $Ea_{(2)} = 370.3477$ kJ/mol. From the previous data, the enthalpy change prices for the two reactions are obtained, namely: $\Delta H_{(1)} = -47.810$ kJ/mol and $\Delta H_{(2)} = -60.545$ kJ/mol. Judging from the price of enthalpy change, path b is more likely because its ΔH value is more exothermic (thermodynamic control), but judging from the price of Ea, reaction a is more likely because $Ea_{(1)} < Ea_{(2)}$ (kinetic control). The observation of Ea is by the experimental results which show that product 1 is the main product (much more in quantity) while product 2 is a by-product.

Study of compounds in the transition state

Transition compound 1. Vibrational frequency data from simulation. The results of computational calculations can display the vibrational modes of transition compounds, where it is obtained that there is one vibrational mode with a negative value, which is -391.622 cm-1. Vibrational modes with negative values indicate a transition state. Visualization of the transition state compound 1 at two different positions is presented in Figure 5. There are 89 vibrational modes of the compound with positive values and there are 6 vibrational modes with zero values.

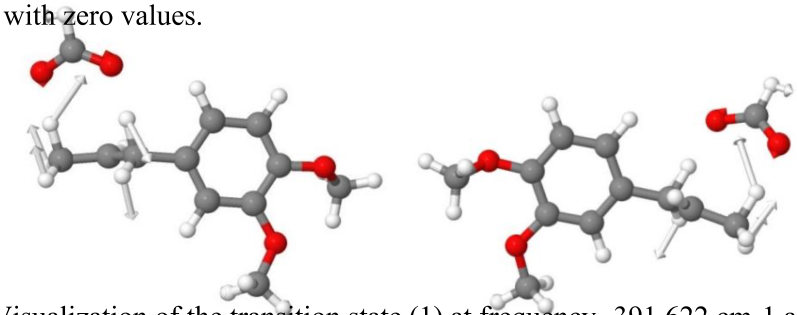


Figure 5. Visualization of the transition state (1) at frequency -391.622 cm-1 at different positions

Transition compound 2. Vibrational frequency data from simulation. The results of computational calculations can display the vibrational modes of the transition compound, where it is obtained that there is one vibrational mode with a negative value, which is -1469.378 cm-1. Vibrational modes with negative values indicate a transition state. Visualization of the transition state compound 2 at two different positions is presented in Figure 6. There are 89 vibrational modes of the compound with positive values and there are 6 vibrational modes with zero values.

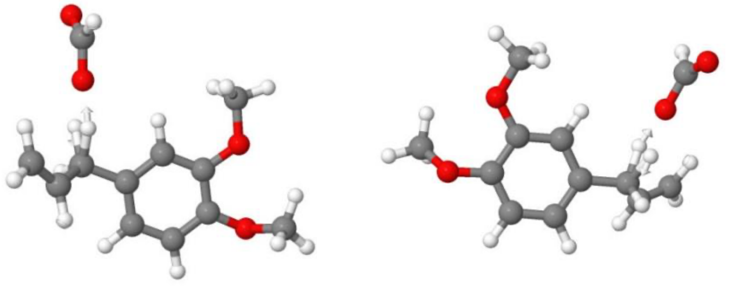
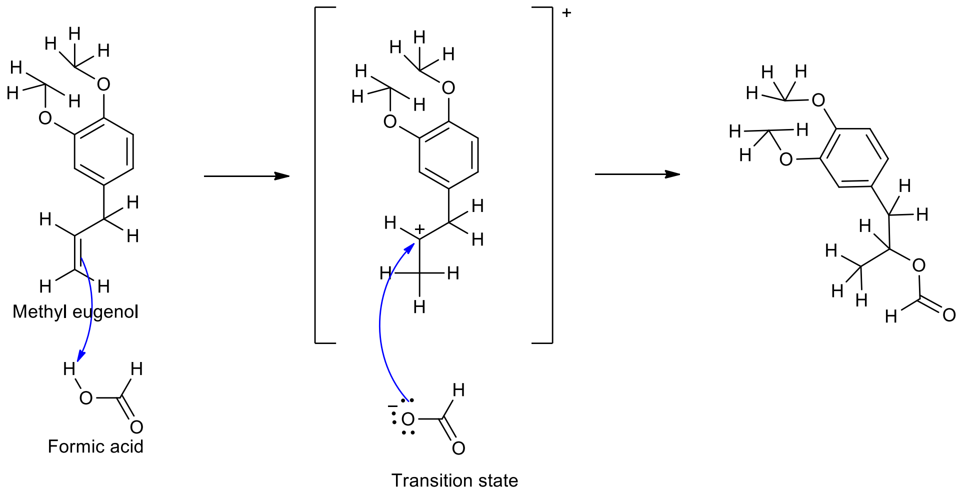


Figure 6. Visualization of transition state 2 at frequency -1469.378 cm-1 at different positions

4.CONCLUSION

Based on the results of laboratory data processing and computational simulations, the following conclusions can be made:

a. The price of the reaction order between methyl eugenol and formic acid to produce methyl eugenol formate ester is order 1 (one).
b. Based on the data from computational calculations, it is obtained that $Ea_{(1)}$ = 163.1937 kJ/mol and $Ea_{(2)}$ = 370.3477 kJ/mol. This fact shows that the formation of polyethylene formate ester compounds through reaction path 1 is more likely than reaction path 2 because $Ea_{(1)} < Ea_{(2)}$.
c. Based on the data from computational calculations, it is obtained that $\Delta H_{(1)}$ = -47.810 kJ/mol and $\Delta H_{(2)}$ = -60.545 kJ/mol. This fact shows that the formation of polyethylene formate ester compound through reaction path 2 is more possible than reaction path 1 because $\Delta H_{(2)} < \Delta H_{(1)}$.
d. The prediction of the reaction path based on the determination of Ea by chemical computation is by the experimental results which show that product 1 is the main product (much more in number) while product 2 is a by-product.
e. The reaction mechanism followed in the reaction between methyl eugenol and formic acid to produce polyethylene formate ester is as follows:



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