A study of the esterification of caffeic acid with methanol using *p*-toluenesulfonic acid as a catalyst

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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 systems is a major limiting factor governing its overall application in the lipid industry. However, the synthesis of methyl caffeate (MC) using CA and methanol is a feasible way to improve its lipophilicity. Herein, the reaction conditions and kinetic parameters for the synthesis of MC using *p*-toluenesulfonic acid (PTSA) as a catalyst were investigated, and the product was confirmed by liquid chromatography–mass spectrometry (LC–MS), Fourier transform infrared (FTIR) and nuclear magnetic resonance (NMR) spectroscopy, and melting point analysis. The highest yield of MC catalyzed by PTSA attained 84.0 % under the optimum conditions as follows: molar ratio of methanol to CA of 20:1, reaction temperature of 65 °C, mass ratio of catalyst to substrate of 8 %, and a reaction time of 4 h. The esterification kinetics of CA and methanol is described by the pseudo-homogeneous second order reversible model. The relationship between temperature and the forward rate constant gives the activation energy of 17.5 kJ mol^{-1}. These results indicated that PTSA possesses high catalytic activity in the synthesis of MC, which is an efficient catalyst suitable for MC production in the chemical industry.

Keywords: caffeic acid; catalysis; esterification; kinetics; methyl caffeate; *p*-toluenesulfonic acid.

INTRODUCTION

Caffeic acid (CA) is one of the most widely distributed hydroxycinnamate and phenylpropanoid metabolites in plant tissues and agricultural wastes.[1,2] Recently, CA, as a natural antioxidant, has received increasing attention with regard to its applications in the food, health, cosmetic and pharmaceutical industries because of its numerous biological activities, such as anti-mutagenic, anti-

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proliferative and anti-oxidant activities.[3–5] However, CA exhibits low solubility and stability in various solvent systems, thus it is necessary to enhance its practical applicability by improving its solubility.[6] The strategy of esterification of hydrophilic CA with lipophilic molecules, such as aliphatic alcohols, could be employed to alter its solubility in hydrophobic media.[7–9] In addition, the synthesis of alkyl esters can significantly improve their function.[10,11] For example, it was found that alkyl esters of CA have a higher antioxidant activity and lipophilicity than CA to protect neuronal PC12 cells against oxidative stress.[12] Therefore, it is advantageous to synthesize alkyl esters of caffeic acid based on both their biological function and potential application.

The classical methods for the esterification of CA, such as Fischer esterification, Wittig and one-pot reactions,[13–15] require tedious operations and generate by-products. Nowadays, a simple reactive approach appeared, *i.e.*, the direct esterification of CA with alcohols. Shin *et. al.* described an esterification of CA in the presence of methanol and sulfuric acid to prepare methyl caffeate (MC). In the reaction, the reaction time was 10 h and the yield achieved was up to 71 %.[13] Sulfuric acid has been widely used as an acid catalyst in a large variety of industrial chemical processes. However, sulfuric acid generally shows weak catalytic activity and requires high reaction temperatures and long reaction time.[16] In addition, the use of sulfuric acid is hazardous and requires special energy-inefficient processes for the treatment of the waste acid.[17] Thus, there is an urgent necessity to find a valid and simple catalyst and esterification system for the efficient synthesis of MC.

Recently, it was shown that *p*-toluenesulfonic acid (PTSA) has the potential to be used as a substitute for conventional acidic catalytic materials.[18] It is characterized by the mildness of the reaction conditions, inexpensive chemical and the excellent functional group tolerance, allowing the formation of the corresponding esters in good to excellent yields.[19] For instance, Jagdale *et al.* performed hydroarylation of cinnamic acids with anisoles and phenols mediated by PTSA under metal and solvent-free conditions, affording 3-(4-methoxyphenyl)--3-phenylpropanoic acids and dihydrocoumarins, respectively, in high yields with excellent selectivity.[20] Therefore, the use of PTSA as a catalyst is potentially attractive for the synthesis of MC.[21] However, a major concern of this system is its sensitivity and instability, because the esters of CA are readily oxidized.[2] Moreover, nowadays, the pseudo-homogeneous model of esterification is a competent kinetic model for predicting an esterification system, taking into account that it is a less complex model.[22,23] Hence, it is necessary to study the reaction conditions and kinetic parameters for an efficient synthesis of MC catalyzed by PTSA.

In the present study, using PTSA as the catalyst, the factors that strongly affect the yield of MC (namely, the reaction temperature, catalyst loading, the mole ratio of methanol to CA, and the ratio of molecular sieve to methanol) were

explored and the corresponding esterification kinetic parameters of CA with methanol were obtained by the pseudo-homogeneous model. Liquid chromategraphy–mass spectrometry (LC-MS), Fourier transform infrared (FTIR) and nuclear magnetic resonance (NMR) spectroscopy, and melting point analysis were used to identify MC in the synthesis product.

EXPERIMENTAL

Materials and reagent

CA (purity > 98 %) was purchased from Nanjing Zelang Pharmaceutical Sci. & Tech. Co. Ltd. (Nanjing, China). Methanol (HPLC grade) and PTSA were purchased from Sinopharm Chemical Reagent Co. Ltd. (Shanghai, China). All other employed solvents and reagents were of analytical grade. Water was purified using an Elga Purelab Option-Q purifycation system (Elga Labwater, High Wycombe, Bucks, UK) and had a resistance greater than 18.0 MΩ cm.

General procedure for MC synthesis

The MC synthesis was performed in 5 mL screw-capped vials containing CA and methanol. The substrate was weighed accurately and the reaction was realized by the addition of PTSA. The reactions were generally performed under the following condition: 1 mM of CA, 20 mM of methanol, 2 % molecular sieves and 6 % PTSA were mixed and reacted at 60 °C under stirring (120 rpm). About 20 μL aliquots of the well-stirred reaction mixture were withdrawn at intervals for analysis.

Kinetics experimental procedure

CA and PTSA were charged into 5 mL screw-capped vials, and then methanol was added. This was taken as zero time for a run. The initial mole ratio of CA and methanol was 1:20, and the total volume of the reactant was 0.8 mL. About 20 μL of liquid sample was withdrawn from the vials at regular intervals for high performance liquid chromatography (HPLC) analysis. In a typical run, about 10 samples were taken from the system. The sample injection volume for the HPLC analysis was 20 μL. All samples were determined in triplicate.

The CA conversion and MC yield were calculated as follows:

$$\text{CA Conversion, \%} = \frac{\text{Consumptive amount of CA, mol}}{\text{Initial amount of CA, mol}} \times 100 \tag{1}$$

$$\text{MC yield, \%} = \frac{\text{Amount of methyl caffeate, mol}}{\text{Initial amount of caffeic acid, mol}} \times 100 \tag{2}$$

LC–MS and HPLC analysis

LC-PAD–MS was realized on a Thermo Fisher LC-MS system. The LC equipment comprised a Finnigan MAT Spectra System P4000 pump, an autosampler with 50 μL loop, a UV6000LP diode array detector, and a Finnigan AQA mass spectrometer. The LC separation was accomplished on a Kromasil C_{18} column (150 mm×4.6 mm, i.d.; 5 μm, W. R. Grace & Co., Deerfield, Illinois, USA) at 40 °C. The mobile phase consisted of solvent A (methanol) and solvent B (water). The samples were eluted isocratically using a 65:35 volume ratio of methanol and water at a flow rate of 1 mL min^{-1}. The wavelength range of the detection was from 200 to 400 nm. The electrospray ionization (ESI) was performed using nitrogen at a flow rate of 1.0 mL min^{-1} to assist nebulization. Selected ion monitoring (SIM) was in the negative ion mode. A capillary voltage at 1.6 kV was used and the temperature of the curved desol-

vation line (CDL) and heat block were both set at 200 °C. The data were processed using Xcalibur 1.2 software.

LC–UV was performed using an LB-5 pump (Beijing Satellite Manufactory, Beijing, China) with a UV detector (L-7420, Techcomp Co. Ltd., Shanghai, China) and N-2000 workstation (Hangzhou Mingtong S&T, Hangzhou, China). The reaction samples were analyzed on a C_{18} column (250 mm×4.6 mm, i.d.; 5 μm, W. R. Grace & Co., Deerfield, Illinois, USA) maintained at 30 °C. The mobile phase consisted of methanol and water (65:35 volume ratio) at a flow rate of 1.0 mL min^{-1}, and the detection wavelength was 325 nm.

FTIR, NMR and melting point analysis of MC

MC was prepared from CA as follows: a solution of CA (9 g) in methanol (100 mL) was treated with a catalytic amount of PTSA and heated at reflux for 6 h. The reaction mixture was cooled to room temperature and concentrated. The residue was dissolved in ethyl acetate and washed successively with dilute saturated aqueous $NaHCO_3$ solution, saturated aqueous NaCl, dried over $MgSO_4$, filtered and evaporated. The residue was crystallized from methanol to give a pure sample (yield 6.3 g, 70 %) as a white solid, and then was identified as MC by FTIR and NMR spectroscopy and melting point determination. Before testing, the sample was dried at 100 °C for 5 h in an oven, and then sealed in plastic bags. A sample was ground into a fine powder using an agate mortar immediately prior to analysis. The FTIR analysis was performed at room temperature on a Nicolet 560 instrument using the KBr disc technique. The ^{1}H-NMR spectra were recorded on Bruker Advance Spectrospin 400 MHz using TMS as the internal standard. The melting point analysis was performed using an Optimelt MPA100 instrument.

RESULTS AND DISCUSSION

LC–MS analysis of the reaction product of CA and methanol

Based on preliminary results, CA had been completely converted to MC after the esterification reaction of CA and methanol catalyzed by PTSA had proceeded for 5 h. The high catalytic efficiency of PTSA was proved *via* LC–MS in the present work. The LC–UV and TIC chromatograms of the reaction mixture from reaction of CA and methanol catalyzed by the PTSA are shown in Figs. 1A and 1B, respectively, which indicated that 84.0 % of the CA was effectively transformed to MC in the presence of methanol. The ESI-MS spectra of the reaction mixture are presented in Figs. 1C and 1D, which exhibit two intense peaks at *m*/*z* 179.01 and 193.07, corresponding to the deprotonated ion [M–H]⁻ of CA and MC, respectively.[24] These results indicated that no side-products were formed during the whole reaction process catalyzed by the PTSA.

FTIR, NMR and melting point analysis

That MC was obtained in the studied reaction was confirmed by FTIR and NMR spectroscopy, and melting point analysis.

M.p.: 159–160 °C. FTIR (KBr, cm^{-1}): 3477, 3099, 2925, 1677, 1606, 1536; ^{1}H-NMR (400 MHz, DMSO-d_6, δ / ppm): 9.60 (1H, *s*, OH), 9.16 (1H, *s*, OH), 7.50 (1H, *d*, *J* = 15.9 Hz, α-H), 7.07 (1H, *d*, *J* = 2.0 Hz, Ph–H), 7.01 (1H, *dd*, *J* =

= 8.1 Hz, Ph–H), 6.77 (1H, *d*, *J* = 8.1 Hz, Ph–H), 6.28 (1H, *d*, *J* = 15.9 Hz, *β*-H), 3.69 (3H, *s*, CH$_3$).
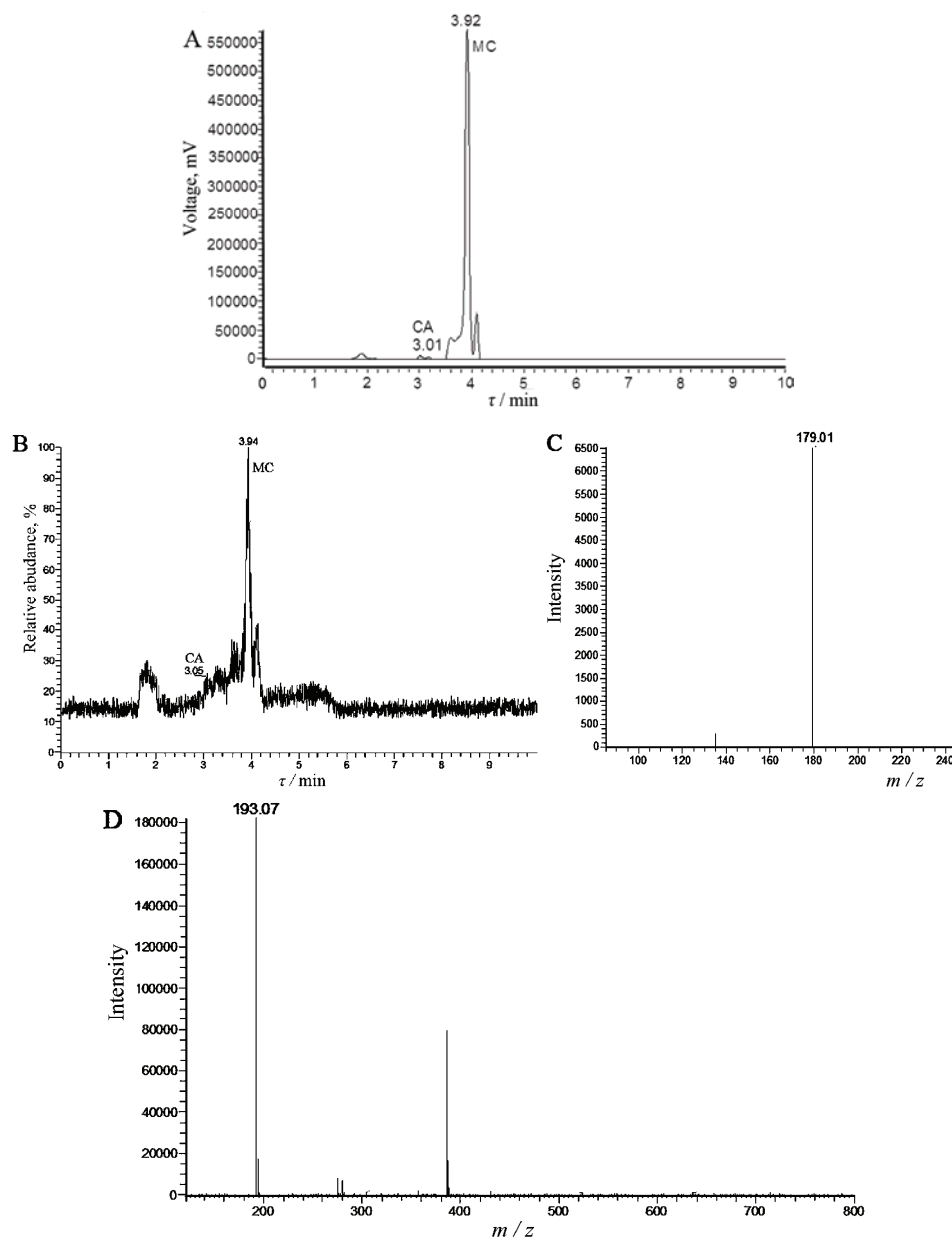

Fig. 1. Analysis of the reaction mixture after CA esterification with methanol catalyzed by PTSA: A) LC–UV chromatogram, B) TIC chromatogram, C) mass spectrogram, *m*/*z* ratio 179.01, and D) mass spectrogram *m*/*z* ratio 193.07.

Effect of mole ratio of methanol to CA on the yield of MC

The esterification reaction between CA and methanol follows a reversible path. A higher equilibrium conversion can only be obtained if the backward reaction is minimized. There are two ways to reduce the rate of backward reaction: a) to remove one of the undesired products, *i.e.*, water in the present case, continuously or b) to use one of the reactants in excess (methanol in this case).[25] In the present system, it was not easy to remove water, as the employed system was a closed system. Thus, the option of using excess methanol was employed in the present study. The change of the MC yield with the mole ratio of methanol to CA is shown in Fig. 2A. The MC yield increased from 25.8 % to 71.7 % on increasing the mole ratio of methanol to CA from 5:1 to 20:1. According to the Le Chatelier principle, the excess methanol was used to shift the equilibrium of the reversible reaction toward the direction of ester formation,[26] while any further increase exhibited an inhibitory effect on the production of MC. At a mole ratio of 50:1, the yield of MC was significantly lower because the use of too high amount of methanol could increase the water content, which arises from commercial methanol.[27] Therefore, the optimal mole ratio of methanol to CA for MC production was suggested to be 20:1.

Effect of reaction temperature on the yield of MC

The reaction temperature is one of the most important parameter affecting the MC yield during the esterification process. Six different temperatures were selected in the range of 45–70 °C. The MC yield markedly increased from 48.9 % to 78.9 % on increasing the temperature from 45 to 65 °C (see Fig. 2B). Obviously, a higher temperature results in an increase in the reaction rate and the equilibrium constant for an endothermic reaction.[17] With a further increase to 70 °C, the final yield of MC decreased to 65.4 %. 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 a temperature leads to methanol volatilization.[28] Therefore, a temperature of 65 °C was retained in the subsequent optimization experiments.

Effect of catalyst loading on the yield of MC

To study the effect of catalyst loading on the yield of methyl ester, the reaction was performed at seven different mass ratios of catalyst to substrate (1, 2, 4, 6, 8 and 10 %), the other reaction conditions being kept constant. The results are shown in Fig. 2C, which indicates that there was a significant increase in the yield of MC as the mass ratio of catalyst to substrate increased from 0 % to 8 %, under identical conditions. The amount of PTSA influences the reaction rate because more H^+ become available when the amount of catalyst in the mixture increases.[29] Unexpectedly, when the mass ratio of catalyst to substrate was in-
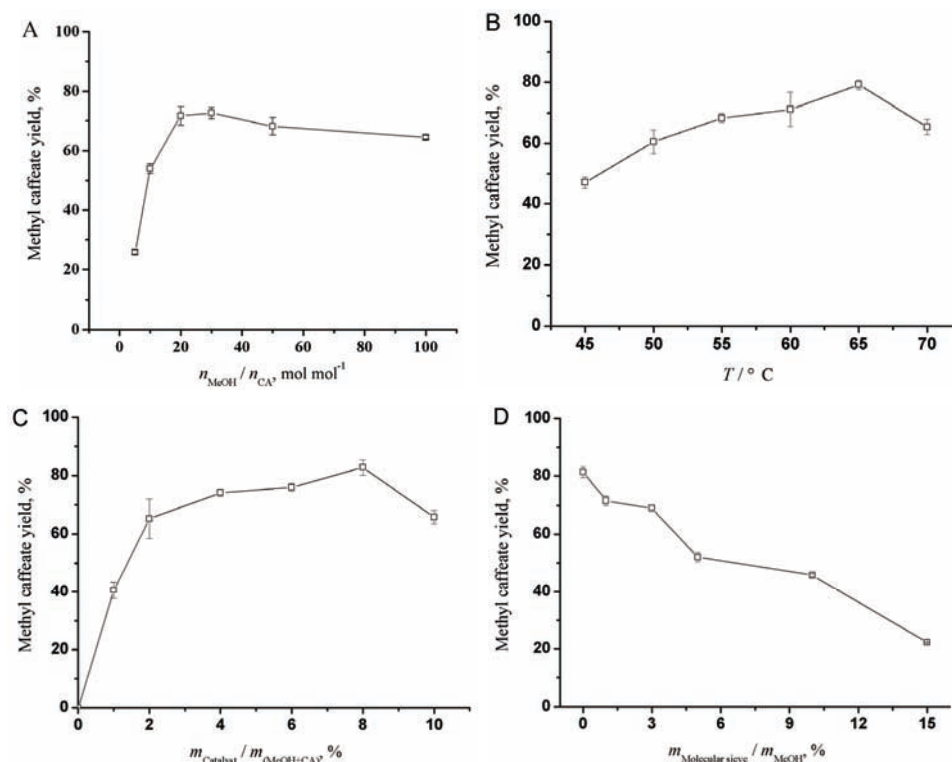
Fig. 2. The effects on the yield of MC of A) the mole ratio of methanol to CA (5:1 to 100:1) at a mass ratio of catalyst to substrate of 6 % and a temperature of 60 °C, B) reaction temperature, C) catalyst loading and D) mass ratio of molecular sieve to methanol, on the yield of MC catalyzed by PTSA. Reaction conditions: B) mole ratio of methanol to CA of 20:1 and a mass ratio of catalyst to substrate of 5 %, C) the catalyst loading (0 to 10 %) at a mole ratio of methanol to CA 20:1 and a temperature of 65 °C and D) the mass ratio of molecular sieve to methanol (0 to 15 %) at a molar ratio of methanol to CA of 20:1, a mass ratio of catalyst to substrate of 8 % and temperature of 65 °C.

creased to 10 %, the yield of MC decreased. Similar results were reported for the synthesis of functionalized pyrimido[4,5-*b*]quinolines and indeno-fused pyrido-[2,3-*d*]pyrimidines in water catalyzed by PTSA.[30] Therefore, the optimum mass ratio of catalyst to substrate for MC synthesis was 8 %.

Effect of mass ratio of molecular sieve to substrate on the yield of MC

Water is the second product during the esterification of CA with methanol. Thus, the water content is another important parameter in esterification reactions. Kumar *et. al.* reported that addition of molecular sieves or silica usually improves the equilibrium conversion.[16] To study the effect of the reaction water on the reaction rate, 0–15 % 3 Å molecular sieves were added to remove the water. Fig. 2D showed that the yield of MC decreased with increasing ratio of molecular

sieve to methanol. This is because PTSA has strong acidic properties and could corrode the molecular sieves in some way. Kuwabara *et. al.* also reported that molecular sieves in many cases had negative effects, such as the formation of di-esters and degradation of unstable substances.[31] Therefore, the employment of molecular sieves to remove the formed water is not suitable here.

Kinetics of the esterification of CA with methanol in the presence of PTSA

The effect of the reaction time on the esterification of CA with methanol catalyzed by PTSA at different temperatures is shown in Fig. 3A. With increasing time, the conversion of CA increased rapidly, which reflects the synthesis ability and stability of MC in the PTSA-catalyzed reaction system. After an esterification time of 4 h, the conversion of CA reached a stable value. Therefore, the optimal reaction time was 4 h. The highest yield of MC was 84.0 % under the optimum conditions as follows: mole ratio of methanol to CA of 20:1, reaction temperature of 65 °C, reaction time of 4 h, and mass ratio of catalyst to substrate of 8 %.
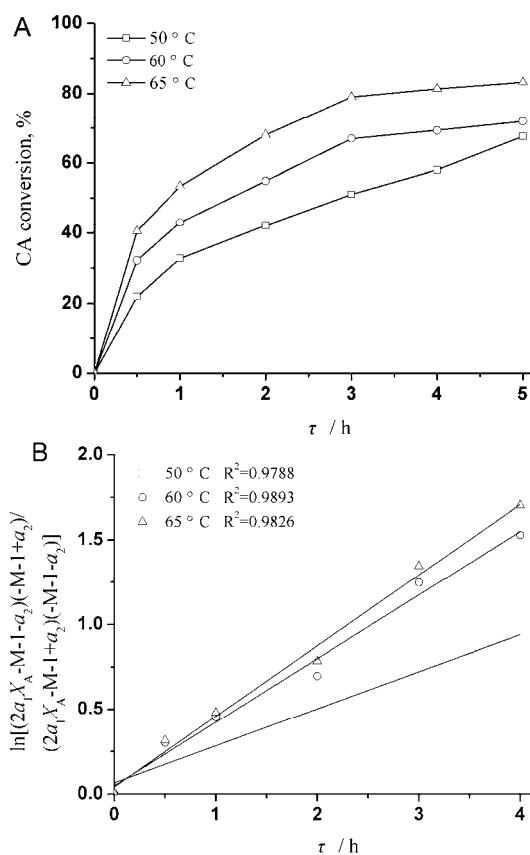

Fig. 3. Second order reversible model for the calculation of the reaction rate constants at different reaction temperatures.

The pseudo-homogeneous model does not take into account the sorption effect into the catalyst in a reactant medium.[32,33] If the reaction mixture is considered as a single liquid phase, the performance of the pseudo-homogeneous model could be considered as a satisfactory tool to correlate the esterification of CA with methanol in the presence of PTSA as a catalyst.

The esterification of CA with methanol using PTSA as a catalyst is represented as follows:

$$A + B \; \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \; E + W \tag{3}$$

where A is CA, B is methanol, E is MC and W is water. This reaction can be considered a second order reaction. Therefore, the rate equation can be written as follows:

$$r_A = \frac{dc_A}{dt} = k_1 c_A c_B - k_{-1} c_E c_W \tag{4}$$

where c_A, c_B, c_E and c_W are the concentrations of CA, methanol, MC and water, respectively. k_1 is the forward rate constant and k_{-1} is the backward rate constant.

From the relationship of c_A and the extent of conversion of CA, x_A:

$$-\frac{dc_A}{dt} = c_{A0} \frac{dx_A}{dt}$$

as well as the correlations of the changes in B, E and W to A:

$$c_A = c_{A0}(1 - x_A)$$
$$c_B = c_{B0}(M - x_A)$$

and

$$c_E = c_W = c_{A0} x_A$$

where c_{A0} is the initial concentration of CA, c_{B0} is the initial concentration of methanol and M is the concentration ratio of methanol to CA ($M = c_{B0}/c_{A0}$).

Thus, Eq. (4) becomes:

$$\frac{dx_A}{dt} = c_{A0}[k_1(1 - x_A)(M - x_A) - k_{-1} x_A^2] \tag{5}$$

At equilibrium, $dc_A/dt = 0$ and thus, the equilibrium constant (K_e) can be calculated from:

$$K_e = \frac{k_1}{k_{-1}} = \frac{x_{Ae}^2}{(1 - x_{Ae})(M - x_{Ae})} \tag{6}$$

x_{Ae} is the conversion of CA at equilibrium stage, and K_e is the equilibrium constant.

If Eq. (6) is integrated and rearranged, the following equation in its linear form is obtained:

$$\ln\left[\left(\frac{2a_1x_A - M - 1 - a_2}{2a_1x_A - M - 1 + a_2}\right)\left(\frac{-M - 1 + a_2}{-M - 1 - a_2}\right)\right] = a_2k_1c_{A0}t \tag{7}$$

where:

$$a_1 = \left(1 - \frac{1}{K_e}\right)$$

$$a_2 = \left[(M + 1)^2 - 4a_1M\right]^{1/2}$$

The results of plotting the left-hand-side of Eq. (7) *vs. t* are presented in Fig. 3B, from which it can be seen that straight lines passing through the origin were obtained. All straight lines gave a good linear correlation lying in the R^2 range of 0.979–0.989. This clearly shows that the proposed kinetic model is appropriate for this reaction. The forward reaction rate constant, k_1, was obtained from the slope of the lines in Figure 3B at different temperatures. The backward rate constants k_{-1} could be calculated using the correlation of the forward rate constant and the equilibrium constant, as in Eq. (7). All forward and backward rate constants at the different reaction temperatures are given in Table I.

TABLE I. Estimated forward and backward rate constants (L mol^{-1} min^{-1}) at different reaction temperatures

Run	Reaction temperature, °C	Forward rate constant, k_1	Backward rate constant, k_{-1}
1	50	0.219	2.992
2	60	0.376	1.749
3	65	0.417	4.344

The dependence of the forward rate constant on the reaction temperature is described by the Arrhenius Law, as given in Eq. (8):

$$k_1 = Ae^{-E/RT} \tag{8}$$

where, A is the pre-exponential factor, E is the activation energy, R is the idea gas constant and T is the reaction temperature (K).

The Arrhenius–Van't Hoff plot of the forward rate constant in the temperature range 50–65 °C gives the coefficient of linearity of 0.940. The slope could be applied to calculate the activation energy. The activation energy is 17.5 kJ mol^{-1}, which confirms that PTSA possesses a high catalytic activity in the synthesis of MC.

CONCLUSIONS

The reaction conditions and kinetic parameters for the efficient synthesis of MC by esterification of CA by methanol using PTSA as a catalyst were first

investigated. The results indicated that the highest attained yield of MC was 84.0 % under the optimum conditions, *i.e*., reaction time of 4 h, reaction temperature of 65 °C, mole ratio of methanol to CA of 20:1, and mass ratio of catalyst to substrate of 8 %. A pseudo-homogeneous second order reversible 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 17.5 kJ mol^{-1}, which indicates that PTSA possesses high catalytic activity in the synthesis of MC.

ИЗВОД

ИСПИТИВАЊЕ РЕАКЦИЈЕ ЕСТЕРИФИКАЦИЈЕ КОФЕИНСКЕ КИСЕЛИНЕ СА МЕТАНОЛОМ У ПРИСУСТВУ *p*-ТОЛУЕНСУЛФОНСКЕ КИСЕЛИНЕ КАО КАТАЛИЗАТОРА

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Кофеинска киселина (КК) представља важан природни антиоксидант. Слаба растворљивост и стабилност КК у различитим растварачима представља главни ограничавајући фактор свеукупне примене у индустрији липида. Због тога синтеза метил-кофеата (МК) из КК и метанола представља могући начин да се побољша липофилност. У оквиру рада, прво су испитани реакциони услови и кинетички параметри синтезе МК користећи *p*-толуенсулфонску киселину (PTSA) као катализатор. У овом раду су прво испитивани реакциони услови и кинетички параметри при синтези МК и за идентификацију производа су коришћене методе LC–MS, FTIR, NMR и анализа тачке топљења. Највећи остварени принос МК у присуству PTSA је био 84 %, а оптимални реакциони услови су били: молски однос метанол: КК 20:1, реакциона температура 65°°C, масени однос катализатор : супстрат 8 %, и реакционо време 4 h. Реакција естерификације КК метанолом је описана ревирзибилним моделом псеудо-хомогеног другог реда. На основу зависности константе k_1 од температуре активациона енергија износи 17,5 kJ mol^{-1}. Резултати показују да PTSA поседује каталитичку активност у синтези МК, као и да је ефикасан катализатор погодан за синтезу МК у хемијској индустрији.

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