Influence of ionic liquid on Novozym 435-catalyzed the transesterification of castor oil and ethyl caffeate

Shangde Sun¹ · Yaping Lv¹ · Sha Zhu¹

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Abstract

Caffeic acid (CA), one kind of phenolic acids widely occurring in the plant kingdom, can be used as potential UV protective ingredient and antioxidant. However, the application of CA was limited because of its unsatisfactory solubility in hydrophilic and lipophilic media. In this work, BMIMPF₆, one kind of ionic liquids (ILs), was developed as an environmental friendly reaction media for the enzymatic preparation of CA derivatives by the transesterification of castor oil (CO) and ethyl caffeate (EC). Different series of ILs with BF₄⁻, TF₂⁻, and PF₆⁻ were screened and compared, and the effects of transesterification variables [temperature (60–100 °C) enzyme concentration (10–90 mg/mL), substrate molar ratio (CO/EC, 1:1–5:1), water load (0–8%), and reaction pressure] were also investigated. Results showed that, in the IL system, hydrophilic and lipophilic products were formed by two competitive reactions [(i) hydrolysis + transesterification and (ii) transesterification]. The maximum hydrophilic caffeoyl lipids yield (26.10 ± 0.28%) and reaction selectivity for hydrophilic caffeoyl lipids (0.4) was achieved in BMIMPF₆ system. The increases of substrate ratio (molar ratio of CO to EC, from 1:1 to 5:1), water load (from 0 to 8%), and enzyme concentration (from 10 to 90 mg/mL) were in favor of hydrophilic caffeoyl lipid formation. However, the vacuum system and high temperature (from 70 to 100 °C) are favorable for lipophilic caffeoyl lipids formation. Under the optimal reaction conditions (90 °C, 75 mg/mL enzyme concentration, substrate ratio 3:1, 60 h, and 10 mmHg vacuum pressures), the maximum EC conversion was 72.48 ± 2.67%. The activation energies of the transesterification, and the selective formations of lipophilic and hydrophilic products were calculated as 44.55, 47.65, and 54.96 kJ/mol, respectively.

Keywords BMIMPF₆ · Ionic liquids · Caffeoyl lipids · Immobilized lipase · Activation energy · Reaction selectivity

Abbreviations

CA	Caffeic acid
CG	Caffeoyl glycerol
CO	Castor oil
CDAG	Caffeoyl di-acylglycerol
CMAG	Caffeoyl mono-acylglycerol
DCG	Dicaffeoyl glycerol
Ea	Activation energies
EC	Ethyl caffeate

HPLC–ESI–MS	High-performance liquid chromatography–electrospray ionization–mass spectroscopy
ILs	Ionic liquids

Introduction

Caffeic acid (3,4-dihydroxycinnamic acid, CA), one kind of phenolic acids consists of phenolic and acrylic groups, is widely distributed in natural plants. CA has some remarkable biological activities, such as inhabitation of melanin formation (Horbury et al. 2016), anti-oxidation (Gulcin 2006), anti-mitosis and anti-cancer (Bailly and Cotelle 2005), which made CA widely used in medicine, health-care product, and cosmetic and food additive industries. However, the high melting point, unsatisfactory solubility, and stability of CA limited its use in many fields (Chen et al. 2011). To overcome this problem, different strategies such as modification

✉ Shangde Sun
sunshangde@hotmail.com

Yaping Lv
lvyaping128@163.com

Sha Zhu
732006138@qq.com

¹ Lipid Technology and Engineering, School of Food Science and Engineering, Henan University of Technology, Lianhua Road 100, Zhengzhou 450001, Henan, People's Republic of China

of phenolic acids have been used (Antonopoulou et al. 2016; Laszlo et al. 2003; Sun et al. 2017; Zhang et al. 2018).

Enzymes have been used as catalysts in many reactions (Chakraborty et al. 2016; Das et al. 2015; Lopresto et al. 2015; Saha et al. 2017a; Sun and Hu 2017; Sun et al. 2017), especially for those thermal sensitivity of phenolic acids (Widjaja et al. 2008; Gao et al. 2015; Yu et al. 2007; Sun et al. 2013). In these previous reports, fatty alcohol (Pang et al. 2013) and phenylethanol (Ha et al. 2013) have been used as caffeoyl acceptors. Castor oil (CO), a renewable resource rich in hydroxy acid, can be obtained from the seed of *Ricinus communis* (Mutlu and Meier 2010), which has lubricity and non-comedogenicity (Cermak et al. 2012), and make it different from the other vegetable oils. In the work, CO was used as the novel caffeoyl acceptor to prepare CA derivatives.

Ionic liquids (ILs), consist of a large asymmetric cation and a diminutive anion, have been known as environmental friendly media as well as catalysts (Vekariya 2017; Rantwijk and Sheldon 2007; Cole et al. 2002; Elgharbawy et al. 2018a; Lunagariya et al. 2017; Ullah et al. 2018; Wang and Sun 2017). Compared with the conventional organic solvents, ILs have many advantages in some extraction processes, for examples, satisfactory stability, high polarity, no vapor pressure, and a wide range of dissolution as well as liquid temperature (Chakraborty et al. 2012; Elgharbawy et al. 2018b; Koo et al. 2006; Katsoura et al. 2009; Liu et al. 2013; Nag et al. 2007; Reilly et al. 2017; Saha et al. 2017b, 2018; Zhao et al. 2002). Moreover, for some enzymatic reaction, ILs can protect enzyme from thermal inactivation and possess excellent reaction selectivity for some enzymatic transesterification (Rantwijk et al. 2003; Housaindokht et al. 2013). Therefore, in some enzymatic reactions, ILs have been used as reaction media instead of the conventional organic solvents (Jain et al. 2005; Pinto et al. 2012; Sun et al. 2018). However, the information about the influence of ILs on the lipase-catalyzed transesterification of CO with ethyl caffeate (EC) to prepare caffeoyl lipids is not available.

In the work, a novel IL system was developed for Novozym 435-catalyzed the transesterification of CO with EC (Fig. 1). Different series of ILs (BF_4^- , PF_6^- , and TF_2N^-) were used as reaction media for the preparation of CO-based caffeoyl lipids. Furthermore, the effects of reaction conditions (substrate ratio, temperature, enzyme concentration, water load, and pressure) on product yield, reaction selectivity for caffeoyl lipids and EC conversion were investigated. Reaction thermodynamics were also evaluated.

Materials and methods

Materials

EC was purchased from Nanjing Ze Lang Pharmaceutical Co., Ltd. (Nanjing, China). CO was provided by Shanghai

Reagent Factory (Shanghai, China). Novozym 435 was obtained from Novozymes A/S (Bagsvaerd, Denmark). All ILs (EMIMBF_4 , BMIMBF_4 , HMIMBF_4 , BMIMTF_2N , EMIMTF_2N , DMIMTF_2N , OMIMPF_6 , $\text{C}_{10}\text{MIMPF}_6$, $\text{C}_{12}\text{MIMPF}_6$, $\text{C}_{14}\text{MIMPF}_6$, EMIMPF_6 , and BMIMPF_6) were purchased from Shang Hai Chengjie Chemical Co., Ltd. (Shanghai, China).

Transesterification in IL system

Different ratios of CO and EC were added into ILs and mixed in a 25 mL round-bottom flask equipped with mechanical stirrer in a thermostatic water bath. Reaction mixtures, including substrates, lipase, and ILs, were incubated at 200 rpm. Samples (10 μL) were withdrawn at regular intervals for the HPLC analysis.

HPLC analysis

Reactants and products were analyzed using HPLC (Waters 1525) with a reverse-phase C18 column (250 $\times$ 4.6 mm, 5 μm). The products were identified with the relevant major ions detected by HPLC–ESI–MS according to the previous report (Sun et al. 2017). Reaction selectivity for the formation of caffeoyl lipids can be defined as the following equations:

$$\text{Reaction selectivity for (CG + DCG)} = \frac{(\text{CG} + \text{DCG})_{\text{yield}}}{\text{EC}_{\text{conversion}}},$$

$$\begin{aligned} \text{Reaction selectivity for (CMAG + CDAG)} \\ = \frac{(\text{CMAG} + \text{CDAG})_{\text{yield}}}{\text{EC}_{\text{conversion}}}. \end{aligned}$$

Statistical analysis

All experiments were carried out at least in triplicate. Results were expressed as mean $\pm$ SEM. Data evaluation was performed using SPSS software for Windows (version rel. 16.0, SPSS Inc., Chicago, IL, USA). The significance of the differences was assessed using variance (ANOVA). Statistical significance was considered at $p < 0.05$.

Results and discussion

Effect of different series of ILs

In the work, three different series of ILs (BF_4^- , PF_6^- , and TF_2N^-) were used as reaction media for the preparation of CO-based caffeoyl lipids (Table 1). EC conversions ($< 3\%$) of ILs system containing BF_4^- were great lower than those of TF_2N^- and PF_6^- ($> 15\%$), which was attributed to the fact that

Fig. 1 Novozym 435-catalyzed the transesterification of castor oil with ethyl caffeate using BMIMPF₆ as reaction solvent

the essential water layer was stripped from Novozym 435 surface by the hydrophilic ILs of BF₄⁻. For ILs with TF₂N⁻, no obvious effect on EC conversion (40–49%) was found with the increase of the chain length of the cations. However, for ILs with PF₆⁻, a significant effect can be found. Among all tested ILs with PF₆⁻, the maximum EC conversion (62.67 ± 2.38%) was obtained in BMIMPF₆ (1-butyl-3-methylimidazolium hexafluorophosphate) system, and a small number of undesired product (CA) (8.89 ± 0.30%) were formed in BMIMPF₆ system. With the increase of chain length of the cation, EC conversion decreased. These phenomena may be ascribed to the longer cation chain of IL and the higher viscosity of reaction system, which resulted in the great mass transfer limitation. These results indicated that hydrophobic ILs with PF₆⁻ or TF₂N⁻ can provide more efficient performance for the reaction of CO with EC. During the caffeoyl structured lipid preparation, two competitive reactions, hydrolysis + transesterification (i) and transesterification (ii), were found as follows (Fig. 1):

The effect of ILs on the two competitive reactions is shown in Table 1. For hydrophobic ILs with TF₂N⁻, reaction selectivity for the hydrolysis of CO to form hydrophilic CG + DCG (reaction i) and the transesterification of CO with EC to form lipophilic CMAG + CDAG (reaction ii) were similar. However, for ILs with PF₆⁻, the effect of ILs on reaction selectivity was different from those of TF₂N⁻, and ILs with PF₆⁻ showed performance for lipophilic CMAG + CDAG selective formation, which was ascribed the

fact that ILs with PF₆⁻ can favor the reaction (ii). Especially for C₁₀MIMPF₆, C₁₂MIMPF₆, and C₁₄MIMPF₆, reaction selectivities for lipophilic CMAG + CDAG were almost four times than that of hydrophilic CG + DCG. When EMIMPF₆ and BMIMPF₆ were used as reaction media, the maximum hydrophilic CG + DCG yields (26.10 ± 0.28%) and reaction selectivity for hydrophilic CG + DCG (0.4) can be achieved. However, the high melt point of EMIMPF₆ (m.p. 58 °C) resulted in the great mass transfer limitation and made the product separation difficult. Therefore, according to the melt point of IL and CG + DCG yield, BMIMPF₆ (m.p. 15 °C) was the most appropriate reaction media for caffeoyl lipid preparation.

Effect of different substrate ratio in BMIMPF₆

The effect of the different substrate ratios on the formation of caffeoyl lipids and EC conversion are shown in Fig. 2.

In BMIMPF₆ system, with the substrate ratio increasing, hydrophilic CG + DCG yield and lipophilic CMAG + CDAG yield both increased (Fig. 2a). Likewise, with the ratio of CO to EC increasing from 1:1 to 5:1, EC conversion and reaction selectivity for hydrophilic CG + DCG and the initial reaction rate all increased (Fig. 2). Interestingly, when the molar content of CO was less than three times that of the EC, lipophilic CMAG + CDAG yields were higher than that of hydrophilic CG + DCG. However, when the substrate ratio

Table 1 Effect of different ionic liquids (ILs) on EC conversion and product yield

ILs	EC conversion (%)	CMAG + CDAG yield (%)	CA yield (%)	CG + DCG yield (%)
BMIMBF ₄	1.22 ± 0.62	0.86 ± 0.20	0	0.36 ± 0.04
EMIMBF ₄	2.31 ± 0.43	1.79 ± 0.15	0.21 ± 0.02	0.32 ± 0.05
HMIMBF ₄	2.84 ± 1.25	2.52 ± 0.82	0	0.32 ± 0.10
BMIMPF ₆	62.67 ± 2.38	32.95 ± 2.62	3.62 ± 0.62	26.10 ± 0.28
EMIMPF ₆	55.67 ± 3.50	35.52 ± 1.37	3.21 ± 0.74	16.94 ± 1.13
OMIMPF ₆	21.91 ± 2.62	13.71 ± 1.62	2.1 ± 0.14	6.1 ± 0.85
C ₁₀ MIMPF ₆	15.82 ± 1.15	11.47 ± 1.25	0.98 ± 0.04	3.37 ± 0.17
C ₁₂ MIMPF ₆	35.82 ± 2.02	23.43 ± 2.62	3.46 ± 0.74	8.93 ± 1.26
C ₁₄ MIMPF ₆	22.54 ± 1.35	16.74 ± 1.02	0.92 ± 0.03	4.88 ± 0.77
HMIMPF ₆	30.31 ± 1.08	15.00 ± 1.32	1.37 ± 0.27	13.94 ± 1.33
BMIMTF ₂ N	41.34 ± 3.52	16.56 ± 1.45	5.93 ± 0.32	18.85 ± 1.45
EMIMTF ₂ N	45.8 ± 1.74	22.58 ± 0.69	2.96 ± 0.34	20.26 ± 2.14
DMIMTF ₂ N	48.93 ± 1.46	22.62 ± 1.34	4.95 ± 0.14	21.36 ± 3.12
HMIMTF ₂ N	39.78 ± 2.36	18.58 ± 2.28	2.83 ± 0.19	18.37 ± 0.70

Reaction conditions: enzyme concentration 75 mg/mL, 80 °C, molar ratio of CO to EC 3:1, ILs 2 mL, and atmospheric pressure, 200 rpm

of CO to EC increased up to $\geq 4:1$, hydrophilic CG + DCG yields were higher than those of lipophilic CMAG + CDAG. The result was attributed to more hydrolysis (competitive reaction i) occurrence with high molar ratio of CO to EC, which can also be confirmed by more by-product CA formation at high substrate ratio of CO to EC ($> 3:1$).

Effect of reaction temperature in BMIMPF₆

With the increase of reaction temperature from 60 to 90 °C, hydrophilic product yield and reaction selectivity for CG + DCG both decreased (Fig. 3a), whereas EC conversion and the initial reaction rate both increased (Fig. 3b). Besides, the time to achieve equilibrium also shortened from > 72 h to 36 h (Fig. 3b). The maximum EC conversion and initial transesterification rate were obtained at 90 °C. When reaction temperature increased up to 100 °C, EC conversion would sharply decreased, which was attributed to the enzyme deactivation at higher temperature (100 °C) of Novozym 435. In comparison with the other Novozym 435-catalyzed reactions (Pang et al. 2013; Kurata et al. 2010; Sun et al. 2009), IL can protect the activity of Novozym 435 at high temperature.

In the transesterification products, the effect of reaction temperature on the formations of CG + DCG and CMAG + CDAG was similar. However, the maximum lipophilic CMAG + CDAG yield ($46.8 \pm 2.1\%$) was obtained at 90 °C, which was higher than the temperature (70 °C) that the maximum hydrophilic CG + DCG yield ($17.2 \pm 1.8\%$) obtained (Fig. 3a). These results showed that high temperature can enhance the transesterification (competitive reaction ii) and suppress the hydrolysis (competitive reaction

i), which was ascribed to the fast removal of water from reaction system at high temperature.

The relationship between initial reaction rate ($\ln V_0$) and reaction temperature ($1/T$) is shown in Fig. 3c. In BMIMPF₆ system, a linear relationship between $\ln V_0$ with $1/T$ was found. From the Arrhenius equation of the transesterification (EC conversion, $\ln V_0 = 4.67 - 5.36/T$), the activation energy (E_a) can be calculated as 44.55 kJ/mol, which was lower than that of solvent-free system (57.60 kJ/mol) (Sun et al. 2017). The E_a of lipophilic CMAG + CDAG and hydrophilic CG + DCG formations were 47.65 and 54.96 kJ/mol, respectively, which were both lower than that of solvent-free system (58.86 and 60.53 kJ/mol) (Sun et al. 2017). These lower E_a were ascribed to the lower viscosity of BMIMPF₆ (450 CP at 25 °C) than that (680CP at 25 °C) of CO, which can decrease the viscosity of reaction system. And BMIMPF₆ has a better solubility for the substrates, which can improve the collision between activated molecules. These can improve the reaction and reduce the activation energy. In the process of the enzymatic reaction of CO with EC in BMIMPF₆, all E_a were higher than those of general enzymatic reactions (0.97–34.5 KJ/mol) (Yadav and Devi 2002), which were due to the great steric hindrance of caffeoyl group.

Effect of different enzyme concentration in BMIMPF₆

In BMIMPF₆ system, the content of lipophilic products in the reaction system increased first and then decreased as the enzyme concentration increased, while the yield of hydrophilic products and the reaction selectivity of CG + DCG

Fig. 2 Effect of different substrate ratio on product yield and reaction selectivity for hydrophilic CG+DCG (a) and EC conversion (b). Conditions: enzyme concentration 75 mg/mL, 80 °C, BMIMPF₆ 2 mL, and atmospheric pressure, 200 rpm

both increased (Fig. 4a). When enzyme concentration increased from 10 mg/mL to 90 mg/mL, EC conversion increased and also the initial transesterification rates linearly increased ($y = 0.1311x$, $R^2 = 0.971$) (Fig. 4b). These results showed that the effect of external mass transfer on the enzymatic reaction using BMIMPF₆ as reaction media can be neglected and it is controlled by kinetic. The maximum yield of CMAG+CDAG (47.78%) was achieved at 75 mg/mL (20%). However, when enzyme concentration increased, reaction selectivity for hydrophilic CG+DCG decreased from 0.07 of 10 mg/mL to 0.35 of 90 mg/mL. These results can be explained by the fact that high enzyme concentration can enhance the hydrolysis to form hydrophilic CG+DCG (competitive reaction i). These results can also be confirmed with the higher E_a of hydrophilic CG+DCG formation (54.96 kJ/mol) than that of lipophilic CMAG+CDAG formation (47.65 kJ/mol).

Fig. 3 Effect of different temperature on product yield, reaction selectivity (a), EC conversion (b), and the relationship between $\ln V_0$ and $1/T$ (c). Conditions: enzyme concentration 75 mg/mL, substrate ratio, 3:1 (mol/mol); BMIMPF₆ 2 mL, and atmospheric pressure, 200 rpm

Effect of water load in BMIMPF₆

During the reaction of CO and EC, two competitive reactions (i) and (ii) were found. It was no doubt that the presence of water can affect the two competitive reactions. And the effect of water load added on lipophilic CMAG + CDAG yield, hydrophilic CG + DCG yield, and reaction selectivity can be found in Fig. 5a. With the increase of water load, lipophilic CMAG + CDAG yield and hydrophilic CG + DCG yield all first increased and then decreased, and the maximum lipophilic product yield and hydrophilic product yield were obtained at 4–6% water load (Fig. 5a). However, reaction selectivity for CG + DCG increased from 0.07 of without water to 0.32 of 8% water load. Moreover, when water was added in the reaction system, more by-product CA was found in the products. The results showed that the presence of water can enhance the competitive reaction (i) (the hydrolysis of CO to form hydrophilic CG + DCG and the formation of CA). Furthermore, the initial

EC conversion can be enhanced in the presence of water added, and EC conversion also increased with the increase of water load added from 2 to 4% (Fig. 5b). However, when water load was $\geq 6\%$, EC conversion decreased. The maximum EC conversion was obtained with 4% water load added. These phenomena can be ascribed to the fact that the presence of water can favor the competitive reaction (i). Excess water in BMIMPF₆ system can dilute the substrates and decrease EC conversion.

Effect of different reaction pressure in BMIMPF₆

The effects of different reaction pressures [atmospheric pressure and vacuum pressure (10 mmHg)] on the reaction of CO with EC in BMIMPF₆ were compared (Fig. 6). The yield of lipophilic product at atmospheric pressure was lower than that of vacuum system, and the yield of lipophilic product at atmospheric pressure without water was also lower than that of atmospheric pressure with 4% water. Besides, reaction

Fig. 4 Effect of enzyme concentration on product yield: reaction selectivity (a) and EC conversion (b). Conditions: 90 °C, substrate ratio 3:1 (mol/mol), BMIMPF₆ 2 mL, and atmospheric pressure, 200 rpm

Fig. 5 Effect of water load on product yield: reaction selectivity (a) and EC conversion rate (b). Conditions: 90 °C, enzyme concentration 75 mg/mL, substrate ratio 3:1, BMIMPF₆ 2 mL, and atmospheric pressure 200 rpm

Fig. 6 Effect of reaction pressure and water load on product yield and reaction selectivity (a) and EC conversion (b). Conditions: 90 °C, enzyme concentration 75 mg/mL, substrate ratio 3:1, BMIMPF₆ 2 mL, and atmospheric pressure 200 rpm

selectivity for hydrophilic products at atmospheric pressure was all higher than that of vacuum system (Fig. 6a). The phenomenon was attributed to that by-product ethanol formed by the reaction (ii) could promote the reaction (i) to synthesize hydrophilic product and CA (>5%). The presence of 4% water in atmospheric pressure system can enhance EC conversion and lipophilic CMAG + CDAG formation. Meanwhile, it can also accelerate the competitive reaction (i) and the synthesis of by-product CA. These results can also be confirmed by the effect of water load (Fig. 5).

Effect of atmospheric pressure and vacuum system (10 mmHg) on the initial EC conversion were similar (Fig. 6b). However, after 36 h, EC conversions of vacuum system were higher than those of atmospheric pressure system. Figure 6b also shows that EC conversion and initial reaction rate were both lower than those [EC conversion, 1.7×10^{-4} mol/(Lmin)] of atmospheric pressure system with

4% water load. These can be ascribed to the acceleration of water on the transesterification in BMIMPF₆ system.

Conclusion

A novel BMIMPF₆ system was successfully exploited for the preparation of caffeoyl lipids. Among all series of tested ILs, BMIMPF₆ can decrease the system viscosity, and showed the best performance for the transesterification, and the maximum hydrophilic CG + DCG yields ($26.10 \pm 0.28\%$) and reaction selectivity for hydrophilic CG + DCG (0.4) can be achieved. The increase of enzyme concentration, substrate ratio, and water load can be in favor of hydrophilic CG + DCG formation. However, the vacuum system and high temperature are favorable for lipophilic CMAG + CDAG formation. In BMIMPF₆ system, the maximum EC conversion ($72.48 \pm 2.67\%$) was obtained under the following conditions: 90 °C, 60 h, enzyme load 75 mg/mL, reactant ratio 3:1 (CO/EC, mol/mol), and 10 mmHg vacuums. Furthermore, according to Arrhenius equation, the E_a for the selective formations of lipophilic products and hydrophilic products and the total transesterification were 47.65, 54.96, and 44.55 kJ/mol, respectively.

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Compliance with ethical standards

Conflict of interest No conflict of interest was declared.

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