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Lipophilic antioxidant dodecyl caffeate preparation by the esterification of caffeic acid with dodecanol using ionic liquid [Hnmp]HSO$_4$ as a catalyst

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Caffeic acid (CA) is widely found in nature, and has a broad spectrum of biological activities. However, the low hydrophilicity and lipophilicity of CA limited its application. Dodecyl caffeate (DC) is the lipophilic ester of caffeic acid (CA), and also has high antioxidant activity. In this work, CA, used as a substrate, and three ionic liquids with different acidities and H$_2$SO$_4$ were used as economic catalysts for DC preparation. The effects of variables on DC yield were investigated and optimized by response surface methodology (RSM). And the kinetic and thermodynamic parameters of the esterification of CA and dodecanol were evaluated. Results showed that lipophilic DC was successfully synthesized using ionic liquid ([Hnmp] HSO$_4$) as a catalyst. And the optimal conditions by RSM were substrate ratio of 10.2 : 1, IL dosage of 9.8% at 87 °C for 118 min. Under the optional conditions, the maximum DC yield was 94.67 ± 1.32%. The k_0, E_a, ΔH, ΔS, and ΔG were 7.18 × 10^7 mol (L min)$^{-1}$, 65.77 kJ mol^{-1}, 63.10 kJ (mol K)$^{-1}$, −103.80 J (mol K)$^{-1}$, and 99.78 kJ mol^{-1} at 363 K, respectively. DC prepared in this work showed a good DPPH radical scavenging activity, which indicated that DC can be used as a potential antioxidant in food and cosmetics.

1 Introduction

Caffeic acid (CA, 3,4-dihydroxycinnamic acid), a phenolic acid of plant secondary metabolites, is widely present in fruits, vegetables, and grains.[1–3] CA has many biological activities such as anti-inflammatory, anti-diabetic, anticancer, antiviral and antioxidant activity *in vitro*.[4–6] Therefore, CA has a broad prospective applications in food, pharmaceutical and cosmetic industries. And the global market and production quantity of CA were about $4.5 × 10^7 and 220 *t* in 2020.[7,8] However, the low oil solubility of CA limits its application.[4,6] These issues can be resolved by the modification of the side chain of CA using long-chain alkyl groups.[9,10] In addition, the reported literatures showed that, the antioxidant activity of alkyl caffeates had a "cut-off" effect, and among these esters, butyl caffeate and dodecyl caffeate (DC) showed the maximum antioxidant activity in oil or emulsion systems.[11–13] Therefore, DC was synthesized in this work.

In the previous reports, some catalysts were used to prepare alkyl caffeate by transesterification or esterification.[14–17] Chen *et al.*[15] and Xiao *et al.*[18] synthesized octyl caffeate using Novozym 435 (2000$ per kg) in an isooctane system for a long time (>52 h). Pang *et al.*[14] reported chemoenzymatic synthesis of propyl caffeate using lipase-catalyzed the transesterification of 1-propanol and intermediate (methyl caffeate). Fiuza *et al.*[16] and Han *et al.*[19] reported that propyl caffeate synthesis was catalyzed by H$_2$SO$_4$ and *p*-toluenesulfonic acid. These previous reports mainly focused on the preparation of short chain ester of alkyl caffeate. However, due to the great steric hindrance, the long chain ester of alkyl caffeate synthesis became very difficult with the increase of carbon numbers of alkyl chains. In our previous report,[20] we prepared octodecyl caffeate by the esterification of caffeic acid-based deep eutectic solvent and octadecanol using cation exchange resin (A-35) as a catalyst, which firstly required the preparation of caffeic acid-based deep eutectic solvent. In this work, we want to develop another cheap catalyst for long chain alkyl caffeate preparation by the simple esterification of CA and dodecanol.

Recently, ILs, due to their negligible volatility, high catalytic activity, low corrosion and combustibility, excellent thermal and chemical stability, and potential for recyclability, had been used as environmentally benign reaction solvents and catalysts.[21–23] In the previous reports, some ILs had also been used as reaction solvents and catalysts for the short chain esters of alkyl caffeate synthesis.[14,24,25] Han *et al.*[26] reported that propyl caffeate was synthesized using IL [BSO$_3$HMIM]TS as a catalyst, and the maximum of propyl caffeate yield was 84%. Recently, due to the strong water absorbability, IL [Hnmp]HSO$_4$ showed good catalytic performance for some esterifications.[27,28] For example, methyl laurate was synthesized using [Hnmp]HSO$_4$.[27] However, IL as a catalyst for the preparation of long chain alkyl caffeate was not available.

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Scheme 1 Structural formula and abbreviations of ILs.

In this work, some ILs (Scheme 1) were prepared by one-step neutralization reaction between cheap heterocyclic compounds (N-methylpyrrolidone (NMP, 20$ per kg), N-methylimidazole (100$ per kg) and pyridine (15$ per kg)) and H_2SO_4. And the ILs were firstly used as dual solvent-catalysts for lipophilic DC preparation by the esterification of CA with dodecanol. The effect of the esterification conditions (temperature, substrate ratio, IL dosage, reaction time, and water content) were optimized by response surface methodology (RSM). The esterification kinetics and thermodynamics also were explored.

2 Experimental section

2.1 Materials

NMP, N-methylimidazole and pyridine were supplied by Aladdin Biochemical Technology Co. Ltd (Shanghai, China). CA was supplied by Zelang Biological Technology Co., Ltd (Nanjing,

China). Dodecanol was purchased from Macklin Biological Technology Co., Ltd (Shanghai, China).

2.2 IL preparation and characteristics

2.2.1 IL preparation. According to the previous methods,[29,30] ILs were prepared as follows. Firstly, H_2SO_4 solution (water : H_2SO_4, 1 : 1, mol : mol) was added dropwise in N-methylpyrrolidone at 5 °C, and the mixture (H_2SO_4 : H_2O : NMP = 1 : 1 : 1, mol : mol : mol) was stirred at room temperature for 24 h. Secondly, the remained NMP in the mixture was removed by washing with ethyl acetate. And then the mixture was dried under vacuum to remove water and ethyl acetate. Finally, N-methylpyrrolidone bisulfate ionic liquid ([Hnmp]HSO_4) was obtained (yield 98.5%). The preparation of N-methyl imidazole bisulfate ionic liquid ([Hmim]HSO_4, yield 97.8%) and pyridine bisulfate ionic liquid ([Hpy]HSO_4, yield 98.2%) were similar to [Hnmp]HSO_4.

2.2.2 IL characteristics. FT-IR spectrum of IL was measured by PerkinElmer Frontier absorption spectrometer for KBr matrix in the wavelength range 4000–400 cm^{-1}. SDT Q600 V20.9 Build 20 thermo-gravimetric analyzer was used for thermogravimetric analysis (TGA) of IL at 5 °C min^{-1} under the protection of N_2. The Hammett acidity of IL was analyzed as follows: different ILs and H_2SO_4 (0.20 mmol L^{-1}) were firstly dissolved in dimethyl yellow-ethanol solution (20 mg L^{-1}), and then the

Table 1 Results of response surface experiments

Run	Temperature X_1 (°C)	Time X_2 (min)	Substrate ratio X_3 (mol mol^{-1})	IL dosage X_4 (%)	DC yield Y (%)
1	90(0)	120(0)	10(0)	10(0)	92.21 ± 0.52
2	90(0)	120(0)	5(−1)	15(1)	71.18 ± 2.13
3	90(0)	120(0)	5(−1)	5(−1)	43.18 ± 1.41
4	90(0)	90(−1)	10(0)	5(−1)	58.05 ± 0.72
5	90(0)	90(−1)	5(−1)	10(0)	57.28 ± 1.56
6	80(−1)	120(0)	10(0)	5(−1)	53.74 ± 1.20
7	80(−1)	150(1)	10(0)	10(0)	85.49 ± 1.84
8	90(0)	90(−1)	10(0)	15(1)	80.38 ± 2.77
9	90(0)	90(−1)	15(1)	10(0)	82.33 ± 1.84
10	100(1)	120(0)	15(1)	10(0)	98.71 ± 0.14
11	90(0)	120(0)	10(0)	10(0)	95.41 ± 0.07
12	90(0)	150(1)	15(1)	10(0)	94.95 ± 1.03
13	90(0)	120(0)	10(0)	10(0)	95.03 ± 0.79
14	90(0)	150(1)	10(0)	15(1)	94.13 ± 0.10
15	100(1)	90(−1)	10(0)	10(0)	89.65 ± 0.87
16	90(0)	150(1)	10(0)	5(−1)	65.78 ± 0.29
17	100(1)	120(0)	5(−1)	10(0)	79.78 ± 0.12
18	80(−1)	120(0)	10(0)	15(1)	90.29 ± 2.23
19	90(0)	120(0)	15(1)	15(1)	93.04 ± 1.96
20	90(0)	120(0)	10(0)	10(0)	95.85 ± 1.18
21	80(−1)	120(0)	5(−1)	10(0)	56.85 ± 0.94
22	90(0)	120(0)	15(1)	5(−1)	74.25 ± 0.44
23	100(1)	120(0)	10(0)	5(−1)	82.01 ± 4.20
24	100(1)	120(0)	10(0)	15(1)	94.85 ± 0.27
25	100(1)	150(1)	10(0)	10(0)	95.27 ± 0.11
26	90(0)	120(0)	10(0)	10(0)	94.42 ± 1.81
27	80(−1)	90(−1)	10(0)	10(0)	67.56 ± 2.98
28	80(−1)	120(0)	15(1)	10(0)	85.49 ± 2.31
29	90(0)	150(1)	5(−1)	10(0)	67.92 ± 2.74

Hammett acidities were determined using a UV-visible spectrophotometer at room temperature.

2.3 Esterification of CA and dodecanol

CA (0.2 g) and dodecanol (2.07 g) were mixed in 10 mL round bottom flasks at 500 rpm and different temperatures (70–100 °C). Then, the IL catalyst was added into the mixture, and the esterification was initiated. Samples (5 μL) were withdrawn at specified times intervals and dissolved in 10 mL methanol. Finally, the mixture was filtered using a microfilter (0.45 nm) for HPLC analysis. DC product was purified by column chromatogram (*n*-hexane/ethyl acetate, 6 : 4).

2.4 Product analysis

Reactant and product were analyzed using a HPLC system. Reaction mixture was eluted by using a reverse-phase C_{18} column (4.6 × 250 mm, 5 μm) at 35 °C, and UV detector was 325 nm. A binary ingredient of water (0.5% acetic acid) and solvent methanol (1 : 19, v : v) was used and eluted at 0.8 mL min^{-1}. DC yield and purify were quantified by external standard method. The structure characterization of DC has been analyzed and was confirmed by the previous reports.[20,31]

2.5 Experimental design

RSM was employed in this study for the verification and prediction of the model equation and was used to optimize the esterification of CA and dodecanol. The independent variables (temperature, time, substrate ratio, and IL dosage) were varied in different levels (−1, 0, and +1) as presented in Table 1.

2.6 Antioxidant activity determination

Antioxidant activity of DC was evaluated by 1, 1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging activity. In brief, 0.1 mL of DC solutions with different concentrations were added to 3.9 mL of 100 μmol L^{-1} DPPH solution in ethanol. The mixtures were shaken vigorously and then placed in darkness for 30 min. The absorbance was measured at 517 nm in a 1 cm quartz cell, and to calculate IC_{50}.

2.7 Statistical analysis

In this study, multiple regression coefficients were employed to predict the linear and interaction effects of the esterification variables. The mathematical relationship between the response and variables was as follows:

$$Y = \beta_0 + \sum_{i=1}^{4} \beta_i X_i + \sum_{i=1}^{4} \beta_{ii} X_i^2 + \sum_{i=1}^{N=3} \sum_{j=i+1}^{4} \beta_{ij} \times X_{ij} \qquad (1)$$

where Y is DC yield; X_i represent variables; all β are constants.

3 Results and discussion

3.1 Screening catalysts

Fig. 1 showed the effect of different ILs on DC yield. Among these ILs, the maximum DC yield (93.03 ± 1.56%) was achieved using [Hnmp]HSO$_4$ at 180 min, which was higher than other ILs

([Hmim]HSO$_4$ 78.33 ± 2.35% and [Hpy]HSO$_4$ 67.71 ± 3.52%) and H$_2$SO$_4$ (41.56 ± 3.10%). Therefore, the catalytic activity (DC yield) of ILs and H$_2$SO$_4$ decreased in an order of [Hnmp]HSO$_4$ > [Hmim]HSO$_4$ > [Hpy]HSO$_4$ > H$_2$SO$_4$. The catalytic activity (DC yield) of H$_2$SO$_4$ was lower than ILs, which was due to that the oxidation of CA in the presence of H$_2$SO$_4$ (<30 min). This phenomenon has also been found in other reactions.[26,29] These indicated that, among all tested ILs, [Hnmp]HSO$_4$ was the best efficient catalyst for the esterification of CA with dodecanol, which was due to that the catalytic activities of ILs were relative to their acidities.[22,26,29] Compared with octadecyl caffeate preparation using cation-exchange resins (24 h, 95.17 ± 2.76%),[20] the time of DC preparation at 85 °C using [Hnmp]HSO$_4$ was reduced to 3 h, which showed that [Hnmp]HSO$_4$ had good performance for DC preparation by the esterification. In our previous work, we also used some immobilized lipases, Novozym 40086, Novozym TLIM, Novozym 435, and *Candida rugose* lipase, to catalyze the esterification to prepare DC. However, no DC product was found. Therefore, [Hnmp]HSO$_4$ was the best catalyst for DC preparation.

3.2 IL characteristics

According to the FT-IR spectra of three ILs, the stretching vibration peaks of S=O and C–N were found at 1037 cm^{-1} and 1151 cm^{-1}, respectively (Fig. 2A). The bands at around 2900–3100 cm^{-1} were related to N–H stretching vibration. However, in [Hnmp]HSO$_4$, a sharp C=O stretching vibration peak was found at 1696 cm^{-1}. The C=C vibration peaks were found at 1615 cm^{-1} in the spectra of [Hmim]HSO$_4$ and [Hpy]HSO$_4$, respectively. These results showed that the three ILs were successfully prepared.[29,32,33]

As shown in Fig. 2B, according to TGA analysis, two weight loss regions of [Hnmp]HSO$_4$ were found at 54 °C and 249 °C, respectively. There were three stages for the thermal decomposition of [Hnmp]HSO$_4$. The first stage was from 25 °C to 82 °C
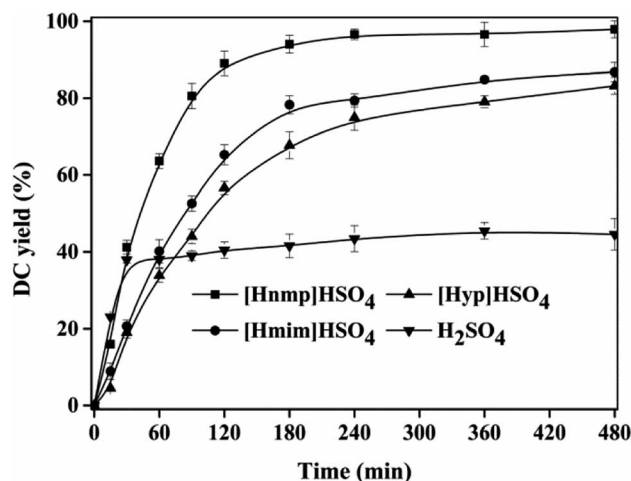

Fig. 1 Effect of different ILs ([Hnmp]HSO$_4$, [Hpy]HSO$_4$, [Hmim]HSO$_4$ and H$_2$SO$_4$) on DC yield. Reactions were conducted with substrate ratio of 10 : 1 (dodecanol to CA, mo mol^{-1}), IL dosage 10% (w/w) with different ILs at 85 °C.
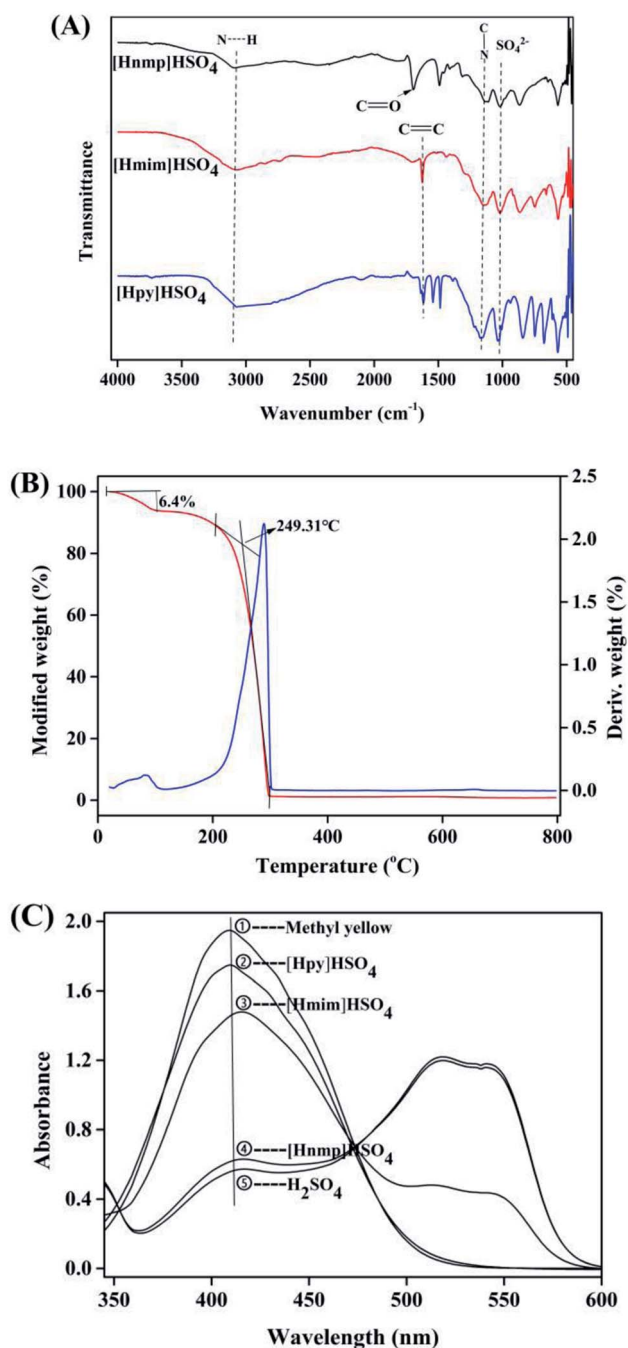
Fig. 2 Characterization of FT-IR ILs; (A) spectra of the three ILs; (B) TG curves of [Hnmp]HSO$_4$; (C) acidity curves of the Brønsted ILs.

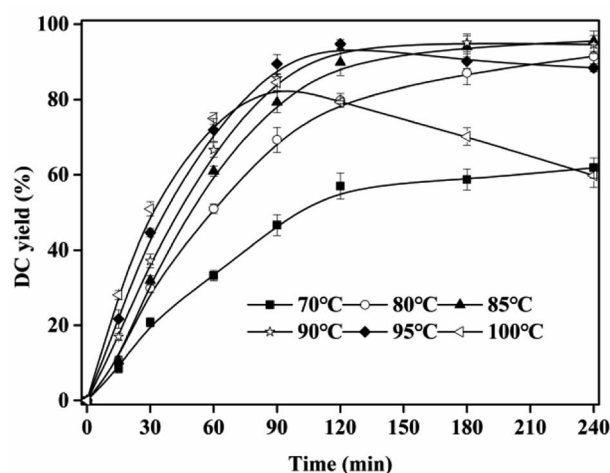

Fig. 3 Effect of reaction temperature on DC yield. Reactions were conducted with IL dosage of 10% and substrate ratio of 10 : 1.

combination of H$^+$ from ILs and dimethyl yellow. The more protonated structures formed indicated the stronger acidity of ILs.[22] Therefore, when the concentrations of different ILs and H$_2$SO$_4$ were same, the acidities decreased as H$_2$SO$_4$ > [Hnmp]HSO$_4$ > [Hmim]HSO$_4$ > [Hpy]HSO$_4$. In the structure of [Hnmp]HSO$_4$, oxygen atom of C=O had high electronegativity, resulting in induction effect. Electrons were pulled to C=O, and the formed hydrogen bond was easily broken and H$^+$ was released. Which resulted in the higher acidity of [Hnmp]HSO$_4$ than other ILs. The acidity and catalytic activity of different ILs were consistent, which indicated that the esterification reaction rate of CA and dodecanol was related to the rate of ILs release H$^+$. This phenomenon has also been found in other esterification reactions catalyzed by ILs.[21,22,29]

3.3 Effect of temperature

The high melting point of CA and great viscosity of IL resulted in the high viscosity of the esterification system. Suitable temperature can decrease the viscosity, and increase DC yield. As shown in Fig. 3, DC yield rapidly increased with temperature at <90 °C. At 120 min, DC yield increased from 54.01 ± 2.48% (70 °C) to 93.03 ± 1.01% (90 °C). This result was ascribed to the fact that, more substrate molecules were activated, and the viscosity of the reaction system decreased at high temperature, which resulted in the high reaction rate. When temperature was higher than 90 °C, DC yield decreased, and the color of reaction system was enhanced, which was due to the oxidization of CA and DC at high temperature (>90 °C). This phenomenon can also be found in another esterification of gallic acid and n-propanol catalyzed by [Hnmp]HSO$_4$.[29]

3.4 Effect of substrate ratio

The esterification of CA with dodecanol was a reversible reaction. High DC yield could be obtained if the reverse reaction was inhibited. Therefore, in this reaction system, excessive
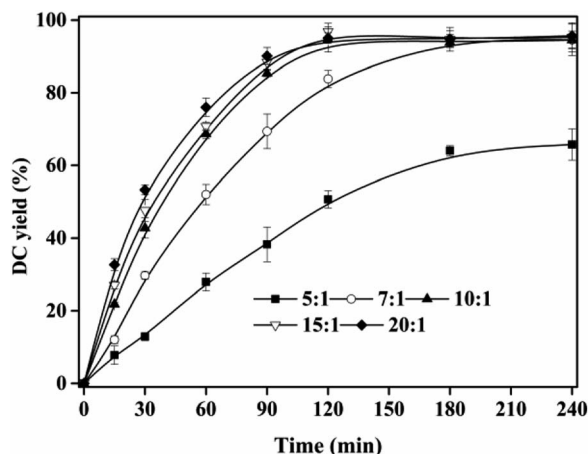
and ~6% weight loss was found, which was mainly due to the evaporation of water. In the second stage from 82 °C to 153 °C, no significant weight loss (<1%) was found. The 3rd stage of the thermal decomposition of [Hnmp]HSO$_4$ was from 153 °C to 296 °C, the great weight loss (93%) was found, which was due to the decomposition of [Hnmp]HSO$_4$. After 296 °C, no significant weight loss of [Hnmp]HSO$_4$ was found.

According to the previous reports,[21,22,29] the acidities of different ILs and H$_2$SO$_4$ were investigated (Fig. 2C). The protonated structure of dimethyl yellow was formed by the

Fig. 4 Effect of substrate ratio on DC yield. Reactions were conducted with IL dosage of 10% at 90 °C.

3.5 Effect of IL dosage

The esterification of CA and dodecanol was a heterogeneous system. The amount of active site of IL catalyst in the reaction system had a significant effect of DC yield. As shown in Fig. 5, with the increase of IL dosage from 3% to 10%, DC yield increased from $35.01 \pm 3.32\%$ to $96.22 \pm 3.18\%$ at 120 min. However, with further increase of IL dosage from 10% to 15%, DC yields decreased, which was due to the increase of DC oxidation with the increase of acidity of reaction system. These indicated that 10% IL dosage was enough for the esterification reaction of CA and dodecanol. Similar results that, the catalyst efficiency per unit of ILs decreased when excess ILs was presented in reaction system, can also be found in other IL-catalyzed reactions.[21,36] Compared with propyl caffeate preparation using $[BSO_3HMIM]TS$ (40% IL dosage),[26] the catalytic activity of $[Hnmp]HSO_4$ (10% IL dosage) to prepare DC was more efficient. Therefore, 10% IL dosage was used in the next experiments.

dodecanol was used, which moved the reaction equilibrium to the formation of DC.

The effect of substrate ratio on DC yield was shown in Fig. 4. When substrate ratio (dodecanol to CA) increased from 5 : 1 to 10 : 1, DC yield rapidly increased from $50.67 \pm 2.37\%$ to $94.71 \pm 3.50\%$ at 120 min, and the equilibrium time was shortened from >240 min to 120 min. In theory, during the esterification, 1 mol of CA is required to react with 1 mol dodecanol to form 1 mol DC and 1 mol water. However, in this work, excessive dodecanol was used to move the esterification towards the formation of DC and avoid the hydrolysis.[34,35] With further increase of substrate ratio up to more than 10 : 1, DC yields were maintained at ~95%. Compared with other enzymatic or chemical synthesis of CA alkyl esters,[14,15,25,26] the equilibrium time for DC preparation was shorter and the substrate ratio was more economic. Therefore, substrate ratio of 10 : 1 was used in the next experiments.
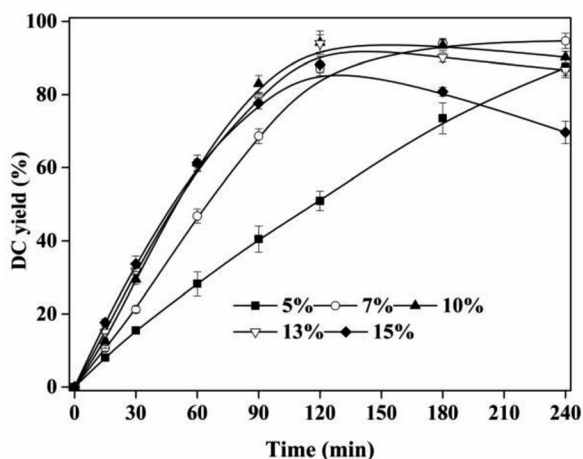

Fig. 5 Effect of IL dosage on DC yield. Reactions were conducted with substrate ratio of 10 : 1 at 90 °C.
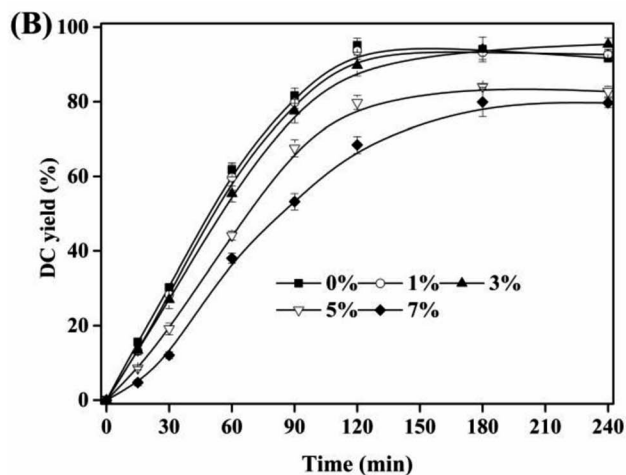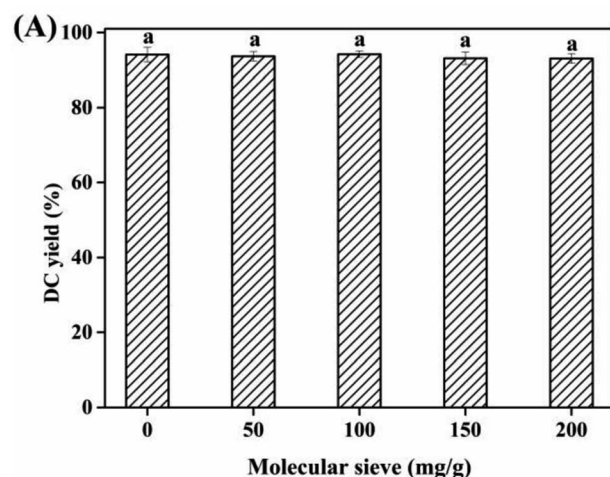
Fig. 6 (A) The comparison of DC yields of 2 h at different molecular sieve load; (B) effect of initial water content on DC yields. The reactions were conducted with substrate ratio of 10 : 1 and IL dosage of 10% at 90 °C. Different letters indicated significant differences ($p < 0.05$).

3.6 Effect of water content

Water was the by-product of the esterification of CA with dodecanol. The effects of molecular sieve added and initial water content on the esterification were shown in Fig. 6. With the increase of molecular sieve load added from 0 to 200 mg g^{-1}, no significant effect of molecular sieve load on DC yield was found (Fig. 6A), which was due to that, (i) the little water formed by the esterification, (ii) reaction substrate was volatilized out of the reaction system at 90 °C, (iii) [Hnmp]HSO$_4$ was a water-tolerable acidic IL.[26] Considering the water content in reaction substrates (dodecanol) and catalyst ([Hnmp]HSO$_4$), the effects of initial water content on DC yield and reaction rate were investigated (Fig. 6B). With the increase of initial water content (<3%), minor influence on DC yield was found. However, the increase of initial water content (>3%), DC yield decreased rapidly from 89.74 ± 2.81% to 68.49 ± 2.45%, which was due to which was due to the inhibition of esterification of CA and dodecanol in the presence of more water. Therefore, the lower initial water content (<3%) was minor influence on the esterification of CA with dodecanol.

3.7 RSM model fitting

RSM was employed to evaluate the interactions of variables and predict optimal DC yield. The design of experiments and results were shown in Table 1. And the quadratic polynomial equation was as follows:

$$\begin{aligned} \text{DC yield (\%)} = {} & 95.80 + 8.49X_1 + 6.01X_2 + 12.86X_3 \\ & + 13.16X_4 - 2.08X_1X_2 - 2.43X_1X_3 - 5.68X_1X_4 \\ & + 1.57X_2X_3 + 2.98X_2X_4 - 1.80X_3X_4 - 3.20X_1{}^2 \\ & - 7.16X_2{}^2 - 11.88X_3{}^2 - 12.07X_4{}^2 \end{aligned} \tag{2}$$

The regression coefficients and significance test of the model were verified by the standard analysis of variance (ANOVA) (Table 2). The quadratic polynomial regression model was extremely significant ($p < 0.0001$). The "Pred R^2" (0.9892) was in reasonable accordance with the "Adj R^2" (0.9959), and the "Lack of Fit" was not significant ($F = 3.21$, $p > 0.05$), which indicated that the model was reliable in predicting the response. The value of R^2 was 0.9980, which was larger than the minimal R^2 of 0.80 for adequate explanation on the variability in the experiments.[34] According to these results, the prediction results of the quadratic model for DC yield were satisfactory.

The p-values of four independent factors indicated that a significant effect on DC yield ($p < 0.0001$) was found, and that the effect order of four independent factors was IL dosage > substrate ratio > temperature > reaction time. Moreover, quadratic terms were also great significant ($p < 0.0001$) for the esterification of CA with dodecanol (Table 2).

3.8 RSM optimization and model verification

Fig. 7 showed the relationship between the interaction effect of variables and DC yield. The increase of temperature with substrate ratio from 9 : 1 to 12 : 1 and reaction time from 110 min to 135 min resulted in the increase of DC yield (Fig. 7a and b). As shown in Fig. 7c, the optimal DC yield appeared at 90 °C to 100 °C and IL dosage from 10% to 12%, and the effect of IL dosage on DC yield was greater than temperature. The optimal DC yield appeared at 110 min to 135 min and substrate from 11 : 1 to 14 : 1 with IL dosage from 12% to 14% (Fig. 7d and e). According to the variance analysis of the regression model, the effects of IL dosage and substrate ratio on DC yield were greater than reaction time (Table 2). The interaction of IL

Table 2 Variance analysis of the regression model

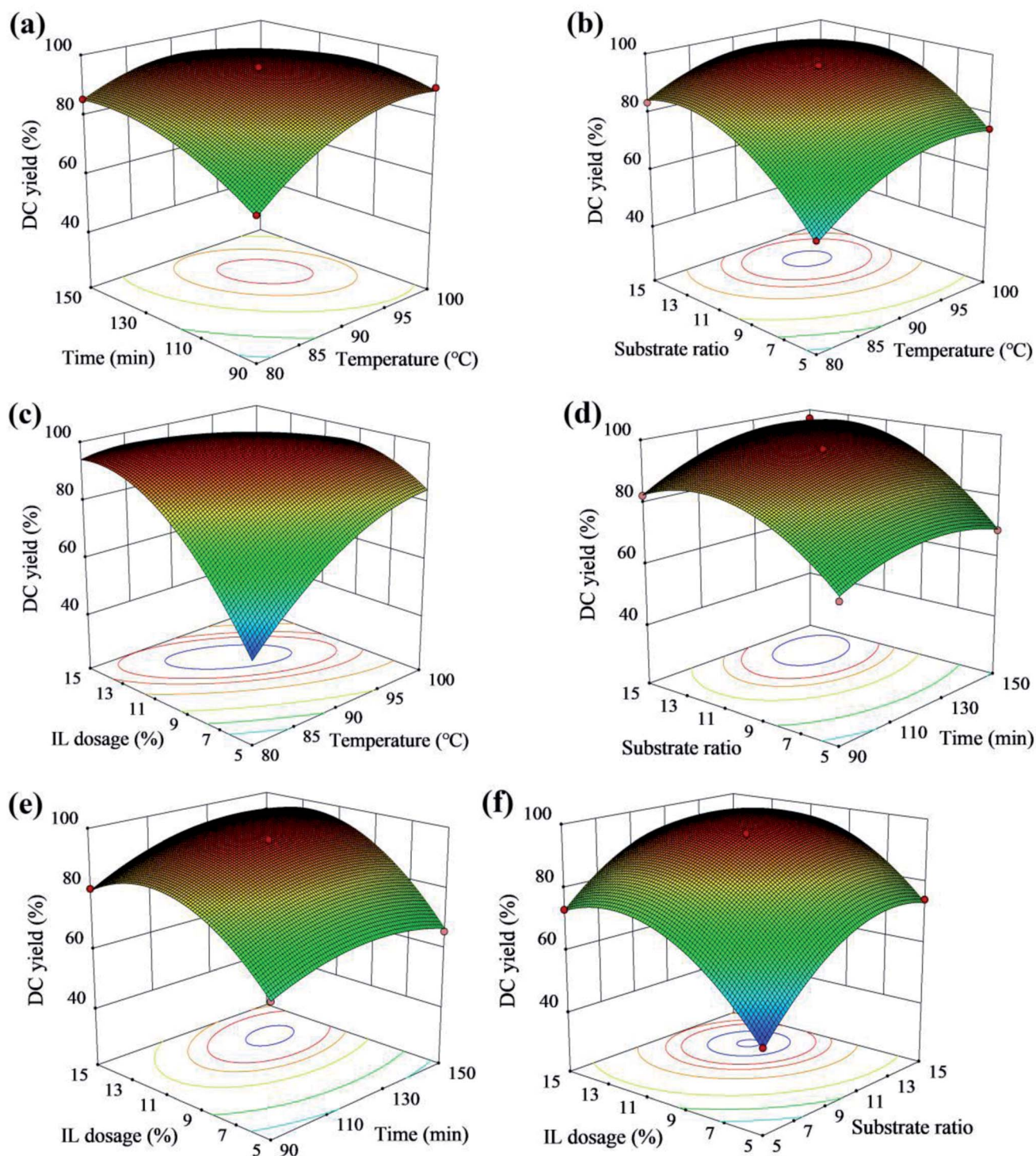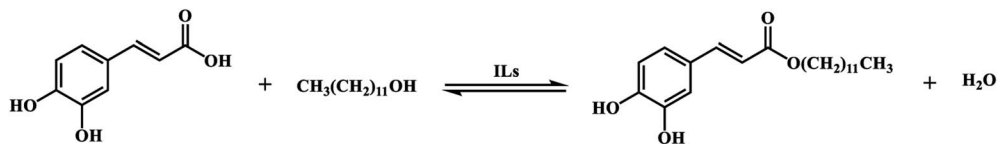| Source	Sum of squares	df	Mean square	F value	p-value prob > F	
Model	7238.41	14	517.03	491.03	<0.0001	Significant
X_1-temperature	575.56	1	575.56	546.61	<0.0001	
X_2-time	340.66	1	340.66	323.53	<0.0001	
X_3-substrate ratio	1357.43	1	1357.43	1289.17	<0.0001	
X_4-IL dosage	1755.57	1	1755.57	1667.28	<0.0001	
X_1X_2	17.31	1	17.31	16.44	0.0012	
X_1X_3	23.55	1	23.55	22.36	0.0003	
X_1X_4	128.88	1	128.88	122.40	<0.0001	
X_2X_3	9.84	1	9.84	9.35	0.0085	
X_2X_4	35.55	1	35.55	33.76	<0.0001	
X_3X_4	13.00	1	13.00	12.34	0.0034	
$X_1{}^2$	66.56	1	66.56	63.21	<0.0001	
$X_2{}^2$	332.96	1	332.96	316.22	<0.0001	
$X_3{}^2$	915.79	1	915.79	869.73	<0.0001	
$X_4{}^2$	944.33	1	944.33	896.84	<0.0001	
Residual	14.74	14	1.05			
Lack of fit	13.11	10	1.31	3.21	0.1364	Not significant
Pure error	1.64	4	0.41			
Cor total	7253.15	28				
R^2	0.9980					

Fig. 7 3D surface of the combined effects of (a) reaction time and temperature; (b) temperature and substrate ratio; (c) temperature and IL dosage; (d) reaction time and substrate ratio; (e) reaction time and IL dosage; (f) substrate ratio and IL dosage on DC yield with the other variables held at a constant level.

dosage and substrate ratio on DC yield was also significant (Fig. 7f).

RSM experiments were performed to find the optimum esterification conditions to maximize DC yield. A quadratic programming model was used to optimize reaction conditions, and the optimized reaction conditions were substrate ratio of 10.2 : 1, IL dosage of 9.8% at 87 °C for 118 min, respectively. Under the optimal variables, the maximum DC yield (94.67 ± 1.32%) was achieved, and it was well accorded with the predicted DC yield (93.75%), which indicated the validation of the

Scheme 2 Esterification reaction of CA with dodecanol.

model. Compared with CA alkyl esters preparation in previous reports (more than 4 h),[14,15,20,24,27] [Hnmp]HSO$_4$ as a catalyst to prepare DC was more efficient (118 min).

Under the optimal variables, other long chain alkyl caffeates, such as, tetradecanol caffeate, hexadecyl caffeate and octadecanol ceffeate, were also synthesized according to the method of DC synthesis, and the yields of these esters were more than 80% (90.16 ± 1.71%, 88.69 ± 0.23% and 80.01 ± 1.23%). These indicated the synthesis method used in this work was also applicable to other long chain alkyl caffeate preparation.

3.9 Kinetic study

According to the relative reports,[35,36] the esterification between CA with dodecanol was a reversible reaction in the presence of IL catalyst [Hnmp]HSO$_4$ (Scheme 2). And the esterification reaction rate equation can be expressed as eqn (3).

$$r = -\frac{dC_A}{dt} = k^+ C_A^\alpha C_B^\beta - k^- C_C^\gamma C_D^\eta \tag{3}$$

where C_A, C_B, C_C, and C_D represented the instant concentration of CA, dodecanol, DC, and water respectively. Where α, β, γ, and η were the reaction orders for A, B, C, and D, respectively. And k^+ and k^- were the forward and reverse reaction rate constants, respectively.

In this work, excessive dodecanol was used to move the reaction equilibrium toward DC formation. Therefore, the concentration dodecanol was considered as a constant, and the reverse hydrolysis was neglected.[37,38] The esterification of CA with dodecanol was considered as a pseudo 1st order.[39] Eqn (3) was as follows:
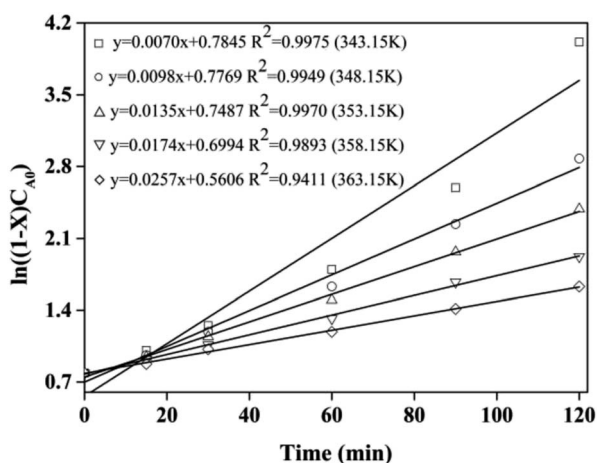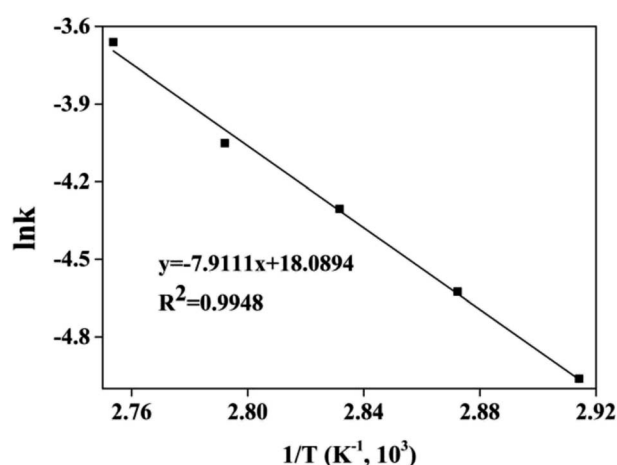
$$-\ln((1 - X)C_{A0}) = kt \tag{4}$$

where k and X are the reaction rate constant (mol (L min)$^{-1}$) and CA conversion (%), respectively.

The plots of $\ln((1 - X)C_{A0})$ *vs.* t at different temperatures (from 70 °C to 90 °C) were obtained. And k_0 and E_a could also be obtained from eqn (5).

$$k = k_0 \exp^{-E_a/RT} \Rightarrow \ln k = \ln k_0 - \frac{E_a}{RT} \tag{5}$$

The kinetic and thermodynamic of the esterification of CA and dodecanol were investigated under the optimized conditions.[27,40,41] Fig. 8 showed the curves of $\ln((1 - X)C_{A0})$ *vs.* t, and the k at different temperatures (from 70 °C to 90 °C) were 7.0 × 10^{-3}, 9.8 × 10^{-3}, 1.35 × 10^{-2}, 1.74 × 10^{-2}, and 2.51 × 10^{-2} mol (L min)$^{-1}$, respectively. These were because the esterification was endothermic and the forward reaction rate was enhanced with the increase of temperature. The regression relationship of $\ln k$ *vs.* $1/T$ was a linear and the regression coefficient (R^2) was 0.9948 (Fig. 9), which indicated that the esterification of CA with dodecanol was a pseudo 1st order reaction. According to Fig. 9, the k_0 and E_a of esterification between CA with dodecanol was calculated as 7.18 × 10^7 mol (L min)$^{-1}$ and 65.77 kJ mol^{-1}, respectively. The k_0 (7.18 × 10^7 mol (L min)$^{-1}$) was notably high, which indicated that the reverse reaction could be ignored in the presence of excessive dodecanol.[42] The E_a of DC synthesis catalyzed by [Hnmp]HSO$_4$ (65.77 kJ mol^{-1}) was lower than solid acid (A-35, 90.19 kJ mol^{-1}).[20] These indicated that [Hnmp]HSO$_4$ catalyst was the best choice for the esterification of CA to dodecanol.

Fig. 8 The curves of $\ln((1 - X)C_{A0})$ *versus* t.

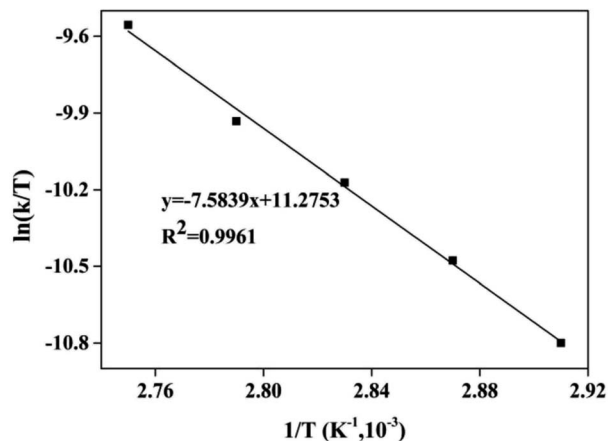**Fig. 9** The curve of $\ln k$ *versus* $1/T$.

Fig. 10 The Eyring curve of $\ln(k/T)$ *vs.* $1/T$.

3.10 Thermodynamic study

Based on the transition state theory, Eyring equation (eqn (6)) was used to relate rate constant to temperature.[40] ΔS and ΔH were calculated from the plot of $\ln(k/T)$ and $1/T$ (eqn (6)). And ΔG was calculated from eqn (7).

$$\mathrm{Ln}\,\frac{k}{T} = -\frac{\Delta H}{R} \times \frac{1}{T} + \ln\frac{k_B}{h} + \frac{\Delta S}{R} \qquad (6)$$

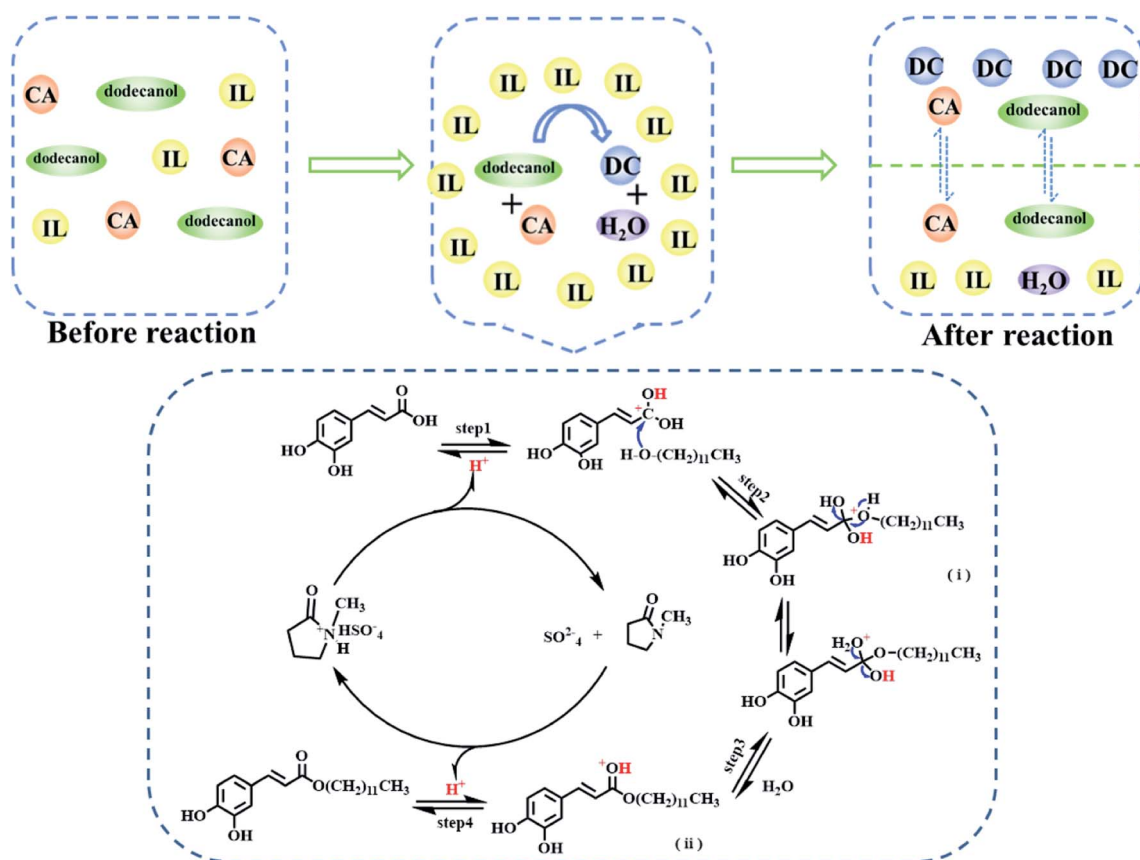$$\Delta G = \Delta H - T\Delta S \qquad (7)$$

where k_B and h are Boltzmann's constant (1.38×10^{-23} J k^{-1}) and Plank's constant (6.626×10^{-23} J s), respectively.

As shown in Fig. 10, the Eyring curve of $\ln(k/T)$ *vs.* $1/T$ had a good linear fit ($R^2 = 0.9961$). The ΔH value of the esterification of CA with dodecanol from the Eyring curve was slightly lower than the E_a (65.77 kJ mol^{-1}) (eqn (8)).

$$\Delta H = E_a - RT \qquad (8)$$

In this work, because the value of RT (eqn (8)) was great lower than the E_a of 65.77 kJ mol^{-1}, the esterification of CA with dodecanol was an endothermic reaction ($\Delta H > 0$). Positive ΔH (63.10 kJ (mol K)$^{-1}$) indicated that heat input was necessary for the esterification of CA with dodecanol to synthesize DC, and also indicated that DC yield increased with the temperature increasing.[40,42]

The negative ΔS (-103.80 J (mol K)$^{-1}$) showed that the esterification of CA and dodecanol had a substantial entropy loss in the formation of IL–substrate complex, which was due to the loss of translational and rotational freedom degrees of reactant and catalytic groups. And negative ΔS (-103.80 J (mol K)$^{-1}$) also indicated the reaction system was more disorder.[42–44] Positive ΔG (99.78 kJ mol^{-1} at 363 K) revealed that the

Scheme 3 The esterification reaction mechanism of CA and dodecanol.

Table 3 Antioxidant activity of DC and well known antioxidants[a]

Antioxidant	IC_{50} ($\mu g\ mL^{-1}$)
TBHQ	20.43 ± 0.58^{b}
BHT	29.93 ± 0.37^{d}
AP	37.48 ± 0.99^{e}
CA	15.18 ± 0.12^{a}
DC	23.41 ± 0.10^{c}

[a] Different letters meant significantly different using ANOVA followed by Duncan's.

esterification of CA with dodecanol was a nonspontaneous process, and also showed that heat input was necessary for DC formation.

3.11 Esterification mechanism

According to the section 3.2 and the previous reports,[29,43,45–48] the esterification mechanism of $[Hnmp]HSO_4$ as a catalyst for DC preparation was proposed in this work (Scheme 3). Firstly, the application of $[Hnmp]HSO_4$ can improve the dissolution of CA in dodecanol to form homogeneous phase before reaction, which made the efficient contact of substrates and $[Hnmp]HSO_4$. H^+ was released from $[Hnmp]HSO_4$, and then H^+ was connected with a carbon atom of the carboxyl group of CA, which can improve the electrophilicity of the carbonyl carbon (step 1) and facilitate the attack of oxygen atom in dodecanol hydroxyl group to form an unstable active tetrahedral intermediate (i) (step 2). The unstable active tetrahedral intermediate (i) was rearranged, and one water and another intermediate (ii) were formed (step 3). Finally, one H^+ was released from the intermediate (iii) to produce DC (step 4). Under this reaction system, product DC and by-product water were produced by the esterification reaction of CA and dodecanol. Due to different interaction, water and $[Hnmp]HSO_4$ were maintained in one phase and DC was automatically transferred to another phase, which promoted the reaction toward DC formation. Therefore, high DC yield was achieved in this reaction system.

3.12 Antioxidant activity of DC

The antioxidant activity of DC was evaluated at 517 nm by DPPH radical scavenging activity, which was compared with TBHQ, BHT, AP, and CA (Table 3). The IC_{50} of these antioxidants were calculated by the linear regressions of plots as follows: AP (37.48 ± 0.99^{e}) > BHT (29.93 ± 0.37^{d}) > DC (23.41 ± 0.10^{c}) > TBHQ (20.43 ± 0.58^{b}) > CA (15.18 ± 0.12^{a}). These results indicated that the DPPH radical scavenging activity of DC was lower that of CA and TBHQ, which were higher than BHT and AP. The number and position of free phenolic hydroxyl groups in these antioxidants was relative to their DPPH radical scavenging activity,[9,49] and the great hindrance of n-dodecyl in DC decreased the DPPH radical scavenging activity of DC, which was lower than of CA. These also indicated that DC can be used as a potential antioxidant in food and cosmetics.

4 Conclusions

In this work, a low cost and easy synthesis $[Hnmp]HSO_4$ showed the best catalytic activity for the esterification of CA with dodecanol to prepare DC. Esterification conditions were optimized by RSM as follows: temperature of 87 °C, substrate ratio of 10.2 : 1, IL dosage of 9.8% and reaction time of 118 min. The maximum DC yield of $94.67 \pm 1.32\%$ was achieved under these conditions. The k_0, E_a, ΔH, ΔS, and ΔG were 7.18×10^7 mol (L min)$^{-1}$, 65.77 kJ mol^{-1}, 63.10 kJ (mol K)$^{-1}$, -103.80 J (mol K)$^{-1}$, and 99.78 kJ mol^{-1} at 363 K, respectively. DC prepared in this work showed a good DPPH radical scavenging activity, which indicated that DC can be used as a potential antioxidant in food and cosmetics.

Author contributions

Xuejing Liu: methodology, date curation, writing – original draft, writing – review & editing. Xiaowei Chen and Hao Zhang: characterization, writing – review & editing. Shangde Sun: methodology, writing – review & editing.

Conflicts of interest

There are no conflicts to declare.

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