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# Thermal esterification of cinnamic and p-methoxycinnamic acids with glycerol to cinnamate glycerides in solventless media: A kinetic model

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## HIGHLIGHTS

- Use of glycerol as reactant and solvent is environmentally friendly.
- Best conditions for the synthesis of monoglycerides of two cinnamic acids are determined.
- Thorough kinetic modelling for both processes is performed.
- Esterification, glycerolysis and disproportionation reactions are involved.
- Removal of water is driven by high temperature and stripping by nitrogen.

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## ABSTRACT

The thermal processes of the esterification of glycerol with cinnamic acid and with p-methoxycinnamic acid in the absence of organic solvents to obtain monocinnamoyl glycerols were studied. Esterification runs were performed batchwise, changing the initial molar ratio of acid to glycerol from 1:3 to 1:9, and temperature from 150 to 200 °C. Under such conditions, systems proved to be monophasic, obtaining almost quantitative acid conversion and a significant selectivity to monoesters (80–90%). Apart from the esterification reactions, experimental conditions and data suggest the presence of glycerolysis and disproportionation reactions. Several kinetic models were fitted to experimental data and statistical and physical criteria were used to select the most adequate: a model with esterification and reversible glycerolysis reactions. When results and parameter values for both acids were compared, their kinetic behaviour in these processes resulted similar in the experimental conditions tested.



## 1. Introduction

Glycerol is a triol with many applications in the chemical, cosmetic, pharmaceutical and food industries. Historically, this compound has been obtained by the saponification of fats and oils and through petrochemical routes. In recent years, the production of biodiesel from edible and non-edible oils and fats has opened a new and more productive route, boosted by energy policies that have promoted the increase of renewable sources to face energy demands, reducing the use of fossil fuels. Glycerol is the major by-product of biodiesel synthesis, which yields approximately 10 wt% of the polyol referred to the biodiesel produced [1]. The increase of glycerol availability has reduced its market prices and, in consequence, awakened the interest of new industrial applications, both for its use as a solvent and a platform chemical [2]. Its structure and functionality allow for its use in many types of processes such as the production of nitro-glycerine, alkyd resins, rosin resins, tri-acetin, 1–3 propanediol, glycerol carbonate, among other products [2]. Esterification processes play an important role in the synthesis of interesting compounds from glycerine. Glycerides and other esters from glycerol and organic acids of different nature have been synthesized using chemical or enzymatic methods, being mono- and di-glycerides important ingredients in cosmetic, pharmaceutical and food industries.

Methoxycinnamic acid and its derivatives act as UV filters in cosmetics and sunscreens [3]. In fact, OMC (2-ethylhexyl-p-methoxicinnamate) is an habitual UV filter in sunscreen formulations [4]. This compound usually exhibits lipophilic characteristics due to its ethylhexyl moiety. However, this feature could lead to excessive transdermal transport thus reducing the amount of the active compound in the epidermis. Some authors have reported on the effects of this compound on the reproductive hormone levels in humans and as an endocrine disruptor [5,6]. To reduce these unwanted effects and promote the primary effects of OMC as sunscreen, strategies based on the use of adequate vehicles are being investigated, including encapsulation and inclusion [7,8]. Moreover, the addition of antioxidants is most adequate to reduce

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**Nomenclature**

| | |
|---|---|
| Abs $\lambda$ | absorbance at wavelength $\lambda$ |
| AIC | Akaike's information criterion |
| BIC | Schwarz's or Bayesian information criterion |
| $C_i$ | concentration of species $i$ (g $L^{-1}$, mol $L^{-1}$) |
| $(E_a/R)k_i$ | ratio of activation energy to $R$ of constant $k_i$ (K) |
| $F_{95}$ | statistical Fischer-$F$ (95% confidence) |
| $k_i$ | kinetic constant $I$ = 1, 2, 3, 4 (L $mol^{-1}$ $min^{-1}$) |
| $K$ | parameter number in kinetic model, Eqs. (1)–(3) |
| $N$ | amount of to which a kinetic model is fitted, Eqs. (1)–(3) |
| $Q$ | flow rate of nitrogen (L $min^{-1}$) |
| $r$ | reaction rate (mol $L^{-1}$ $min^{-1}$) |
| $R$ | ideal gas constant (8314 J $mol^{-1}$ $K^{-1}$) |
| RMSE | square root of the mean squared error |
| $t$ | time (min) |
| $T$ | Temperature (°C or K) |
| $X$ | conversion value |
| $y$ | dependent variable in $F_{95}$, SQR, AIC and AICc parameters, Eqs. (5–7) |

*Greek letters*

| | |
|---|---|
| $\omega$ | Stirrer rotation rate ($s^{-1}$) |
| $\varepsilon$ | relative error of the concentration of diesters |

*Compounds (normal text and subscripts)*

| | |
|---|---|
| A | acid (cinnamic or p-methoxycinnamic acid) |
| C | cinnamic acid |
| G | glycerol |
| MG | monocinnamyl glycerols |
| DG | dicinnamyl glycerols |
| W | water |

*Subscripts*

| | |
|---|---|
| 0 | relative to the preexponential term in the Arrhenius equation, residence time of the solvent peak or initial conditions |
| 1 | relative to the reaction of esterification between glycerol and cinnamic acid |
| 2 | relative to the reaction of esterification between monocinnamyl glycerol and cinnamic acid |
| 3 | relative to the reaction of glycerolysis between dicinnamyl glycerol and glycero |
| 4 | relative to the reaction of disproportionation between two molecules of monocinnamyl glycerol |
| calc, $c$ | calculated variable value using a kinetic model |
| exp, $e$ | experimental value |

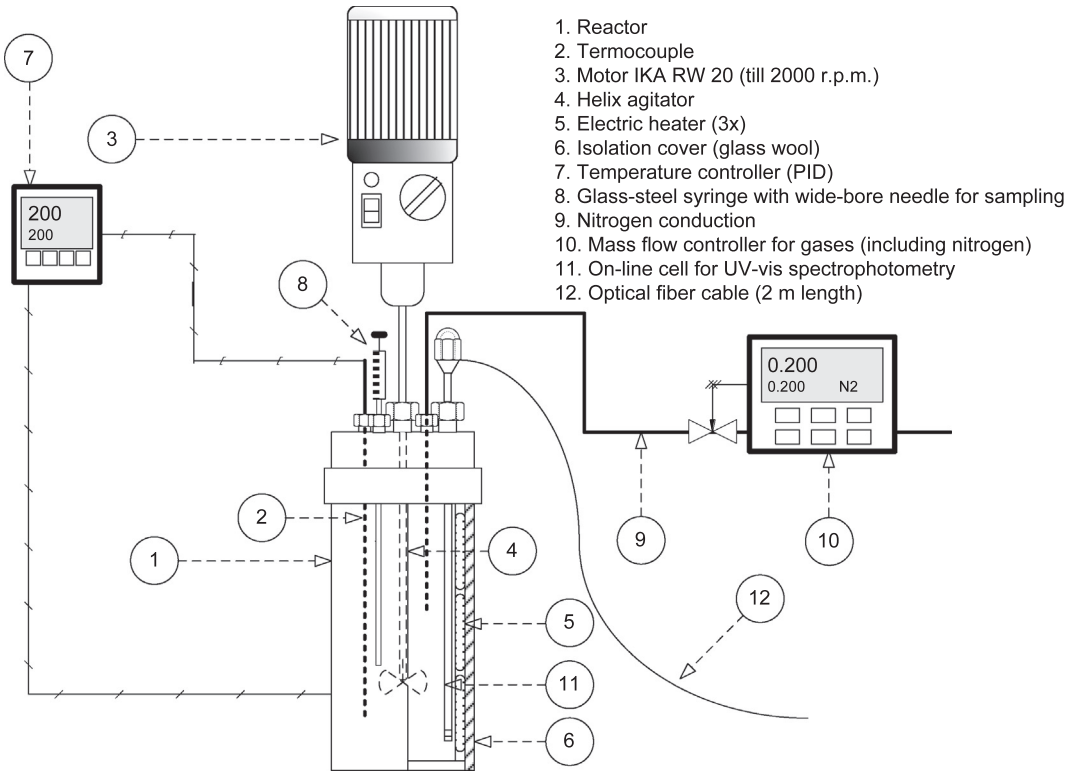


**Fig. 1.** Set-up for solubility tests and thermal esterification runs with glycerol and both cinnamic and methoxycinnamic acids.

ROS production and, therefore, skin aging [9,10]. A novel alternative to add to the current UV-filter array are new and more hydrophilic cinnamates obtained from esterification of p-methoxycinnamic acid with glycerine and other polyols [4].

Cinnamic acid or benzenepropenoic acid and its derivatives are ubiquitous in the plant kingdom and have many properties as antioxidants, antimicrobials, antivirals and antiparasitics that render them very useful in the pharmaceutical, food and cosmetic

**Table 1**
Experimental conditions of kinetic runs. Common experimental conditions: $Q$ ($N_2$) = 0.2 L min$^{-1}$, $\omega$ = 250 r.p.m.

| Acid | Run | $C_G$ (mol L$^{-1}$) | $C_A$ (mol L$^{-1}$) | $C_A/C_G$ | $T$ (°C) |
|---|---|---|---|---|---|
| Cinnamic | RLC1 | 8.88 | 2.96 | 1/3 | 150 |
| | RLC2 | 10.8 | 1.80 | 1/6 | |
| | RLC3 | 11.61 | 1.29 | 1/9 | |
| | RLC4 | 8.88 | 2.96 | 1/3 | 180 |
| | RLC5 | 10.8 | 1.80 | 1/6 | |
| | RLC6 | 11.61 | 1.29 | 1/9 | |
| | RLC7 | 8.88 | 2.96 | 1/3 | 200 |
| | RLC8 | 10.8 | 1.80 | 1/6 | |
| | RLC9 | 11.61 | 1.29 | 1/9 | |
| p-Methoxy cinnamic | RLM1 | 10.32 | 1.72 | 1/6 | 150 |
| | RLM2 | 11.25 | 1.25 | 1/9 | |
| | RLM3 | 8.28 | 2.76 | 1/3 | 180 |
| | RLM4 | 10.32 | 1.72 | 1/6 | |
| | RLM5 | 11.25 | 1.25 | 1/9 | |
| | RLM6 | 8.28 | 2.76 | 1/3 | 200 |
| | RLM7 | 10.32 | 1.72 | 1/6 | |
| | RLM8 | 11.25 | 1.25 | 1/9 | |

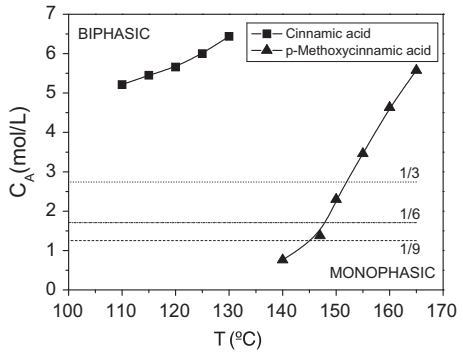


**Fig. 2.** Solubility of cinnamic and methoxycinnamic acids in glycerol at several temperatures.

industries. Flavours with antimicrobial properties are synthesized from cinnamic acid and its derivatives [11]. This acid is also widely used in fragrances (shampoos, bath soaps and detergents) [12]. Esters of glycosides and cis-cinnamic acid are being studied due to their natural herbicidal activity [13]. The use of cinnamic acid and its derivatives in traditional medicine holds a long history, and research in this field has been increased during the last years as a consequence of a renewed interest in natural resources. There is a reawakened concern in the synthesis of new drugs from cinnamic acid to treat several kinds of cancer and tuberculosis [14–16].

Kinetic studies on esterification are plentiful, with a huge increase in the last years regarding esterification and related reactions for biomass valorisation, new catalysts for green processes and process intensification. Most of the studies are focused on catalytic processes: acid, basic and enzymatic [17,18]. Some works approach microwave, ultrasound and supercritical enhancement of classical thermal processes developed in the first part of the last century [19]. There are a number of reactions taking place at the same time in esterification and transesterification processes involving triglycerides, including glycerolysis, hydrolysis and disproportionation of glycerides [20,21]. In esterification kinetics, with the exception of some enzymatic syntheses, it is very common to find potential kinetic model with first-order behaviour toward both reagents: alcohol and acid [22,23]. There are cases where the evolution of reagent concentrations is of first-order nature: saturation of the phase with a reagent (for example, glycerol is slightly soluble on most common organic solvents), huge excess of a reagent or kinetic control due to physical phenomena like mass transfer [24–26].

The aim of this work is to perform a kinetic study of the esterification of glycerol with cinnamic and p-methoxycinnamic acids in conditions where glycerol acts both as solvent and reagent. Preliminary runs were conducted to establish the solubility of the

**Table 2**
Effects of a nitrogen inert atmosphere and stirring rate on the thermal esterification of glycerol and cinnamic acid on conversion and selectivity to mono-cinnamoyl glycerol. Conditions: $T$ = 200 °C, $C_G/C_c$ = 3/1, $X \sim 1$ ($t_r$ = 1440 min), $\omega$ = 250 r.p.m.

| Parameters | Runs | | |
|---|---|---|---|
| | Without $N_2$ | $Q$ ($N_2$) = 0.2 L/min bubbles | $Q_{N2}$ = 0.2 L/min blanket |
| $X_A$ | 0.85 | 0.97 | 0.99 |
| $X_{MG}$ | 0.70 | 0.67 | 0.75 |
| $X_{DG}$ | 0.15 | 0.30 | 0.23 |
| $Abs_{275\ nm}$ | 0.52 | 0.98 | 1.12 |
| $Abs_{420\ nm}$ | 1.56 | 0.31 | 0.03 |

| Parameters | $Q$ ($N_2$) | | | |
|---|---|---|---|---|
| | 0.05 L/min | 0.2 L/min | 0.5 L/min | 1.0 L/min |
| $X_A$ | 0.99 | 0.99 | 0.99 | 0.99 |
| $X_{MG}$ | 0.76 | 0.75 | 0.72 | 0.65 |
| $X_{DG}$ | 0.23 | 0.23 | 0.25 | 0.33 |
| $Abs_{275\ nm}$ | 1.02 | 1.12 | 1.12 | 1.13 |
| $Abs_{420\ nm}$ | 0.04 | 0.03 | 0.04 | 0.03 |

| Parameters | $\omega$ | | | | |
|---|---|---|---|---|---|
| | 0 s$^{-1}$ | 4.16 s$^{-1}$ | 8.32 s$^{-1}$ | 13.13 s$^{-1}$ | 20 s$^{-1}$ |
| $X_A$ | 0.95 | 0.99 | 0.99 | 0.99 | 0.99 |
| $X_{MG}$ | 0.72 | 0.75 | 0.73 | 0.72 | 0.69 |
| $X_{DG}$ | 0.22 | 0.23 | 0.24 | 0.25 | 0.27 |
| $Abs_{275\ nm}$ | 1.13 | 1.12 | 1.06 | 0.98 | 0.93 |
| $Abs_{420\ nm}$ | 0.03 | 0.03 | 0.04 | 0.12 | 0.15 |

**Table 3**
Kinetic models tested to fit experimental data for the esterification of both cinnamic and methoxycinnamic acids with glycerol.

| Model number | Rate equations | Reaction pathway |
|---|---|---|
| 1 | $r_1 = k_1 C_A C_G$<br>$r_2 = k_2 C_A C_{MG}$ | $A + G \xrightarrow{r_1} MG + W$ |
| 2 | $r_1 = k_1 C_A$<br>$r_2 = k_2 C_A$ | $A + MG \xrightarrow{r_2} DG + W$ |
| 3 | $r_1 = k_1 C_A C_G$<br>$r_2 = k_2 C_A C_{MG}$<br>$r_3 = k_3 C_G C_{DG}$ | $A + G \xrightarrow{r_1} MG + W$ |
| 4 | $r_1 = k_1 C_A$<br>$r_2 = k_2 C_A C_{MG}$<br>$r_3 = k_3 C_{DG}$ | $A + MG \xrightarrow{r_2} DG + W$<br>$DC + G \xrightarrow{r_3} 2MG$ |
| 5 | $r_1 = k_1 C_A C_G$<br>$r_2 = k_2 C_A C_{MG}$<br>$r_3 = k_3 C_G C_{DG}$<br>$r_4 = k_4 C_{MG}^2$ | $A + G \xrightarrow{r_1} MG + W$ |
| 6 | $r_1 = k_1 C_A$<br>$r_2 = k_2 C_A C_{MG}$<br>$r_3 = k_3 C_{DG}$<br>$r_4 = k_4 C_{MG}^2$ | $A + MG \xrightarrow{r_2} DG + W$<br>$DG + G \xrightarrow{r_3} 2MG$<br>$2MG \xrightarrow{r_4} DG + G$ |
| 7 | $r_1 = k_1 C_A$<br>$r_2 = k_2 C_A C_{MG}$<br>$r_3 = k_3 C_W C_{MG}$<br>$r_4 = k_4 C_W C_{DG}$<br>$r_5 = k_5 C_W$ | $A + G \xrightarrow{r_1} MG + W$<br>$A + MG \xrightarrow{r_2} DG + W$<br>$MG + W \xrightarrow{r_3} A + G$<br>$DG + W \xrightarrow{r_4} A + MG$<br>$W \xrightarrow{r_5} W(g)$ |

**Table 4**
Fitting statistical criteria of the kinetic models fitted to experimental data from the esterification processes of glycerol and cinnamic and methoxycinnamic acids.

| Acid | Model number | $N/K$ | $F_{95}$ | AIC | BIC | $\varepsilon_{max}$ for $C_{DG}$ (%) | RMS error |
|---|---|---|---|---|---|---|---|
| Cinnamic | 1 | 167 | 70,484 | −2565 | −3.81 | 80 | 0.23 |
| | 2 | 167 | 69,390 | −2643 | −3.93 | 80 | 0.24 |
| | 3 | 111 | 58,552 | −2795 | −4.14 | 80 | 0.21 |
| | 4 | 111 | 51,049 | −2774 | −4.11 | 80 | 0.22 |
| | 5 | 84 | 110,737 | −3260 | −4.83 | 60 | 0.14 |
| | 6 | 84 | 62,346 | −3077 | −4.55 | 70 | 0.18 |
| | 7 | 67 | 44,552 | −3041 | −4.49 | 80 | 0.18 |
| p-Methoxy cinnamic | 1 | 156 | 39,013 | −2319 | −3.69 | 85 | 0.30 |
| | 2 | 156 | 40,306 | −2360 | −3.75 | 85 | 0.29 |
| | 3 | 104 | 51,456 | −2871 | −4.56 | 80 | 0.21 |
| | 4 | 104 | 49,658 | −2845 | −4.52 | 80 | 0.21 |
| | 5 | 78 | 52,373 | −2955 | −4.68 | 55 | 0.18 |
| | 6 | 78 | 50,137 | −2892 | −4.58 | 65 | 0.19 |
| | 7 | 62 | 16,152 | −2417 | −3.80 | 85 | 0.29 |

**Table 5**
Kinetic parameters of the kinetic models fitted to experimental data from the esterification processes of glycerol and cinnamic and methoxycinnamic acids.

| Kinetic parameters | Cinnamic acid | | p-Methoxycinnamic acid | |
|---|---|---|---|---|
| | Value | SE | Value | SE |
| Ln $k_{10}$ | 13.3 | 0.4 | 16.6 | 0.7 |
| $(E_a/R)^{k1}$ | 9623 | 176 | 11,139 | 322 |
| Ln $k_{20}$ | 14.8 | 0.5 | 16.4 | 0.8 |
| $(E_a/R)^{k2}$ | 9739 | 198 | 10,362 | 362 |
| Ln $k_{30}$ | 26.2 | 1.3 | 24.8 | 1.7 |
| $(E_a/R)^{k3}$ | 15,702 | 605 | 14,978 | 777 |
| Ln $k_{40}$ | 47.2 | 6.3 | 29.2 | 6.2 |
| $(E_a/R)^{k4}$ | 26,154 | 2999 | 17,802 | 2948 |

acids in the polyol and the effect of using a nitrogen inert atmosphere on the conversion of each acid and yield to the monoesters. Afterwards, kinetic runs were performed to study the effects of the main variables, namely: acid to polyol molar ratio and temperature. Experimental data were used to fit three proposed kinetic models and select the most appropriate, comparing, finally, the models selected for both acids.

## 2. Materials and methods

### 2.1. Materials

For the preliminary and kinetic runs, the following reagents were used: trans-4-methoxycinnamic acid (98%) (Alfa Aesar), extra pure glycerol (99%) (Scharlau Chemie S.A.), trans-cinnamic acid (99%) (Alfa Aesar), and HPLC-grade methanol (Fisher Scientific UK Ltd.).

### 2.2. Methods

#### 2.2.1. Preliminary experiments

A series of preliminary runs were undertaken with cinnamic acid to determine operating conditions leading to a monophasic system where oxidation reactions would be minimised. Therefore, several factors were taken into account: agitation, acid solubility in glycerol, and the introduction of a nitrogen stream in the reactor.

The solubility study was performed in the experimental set-up used in all esterification runs, depicted in Fig. 1. It consisted of a stainless steel vessel heated by resistors located around it. The lid had several connections that allowed for the introduction of a nitrogen stream, the agitation helix, a thermocouple, a syringe with a wide-bore needle for sampling and, for the solubility studies, an off-line immersion probe connected to a spectrophotometer JASCO V-630 using an optical fibre cable. The temperature

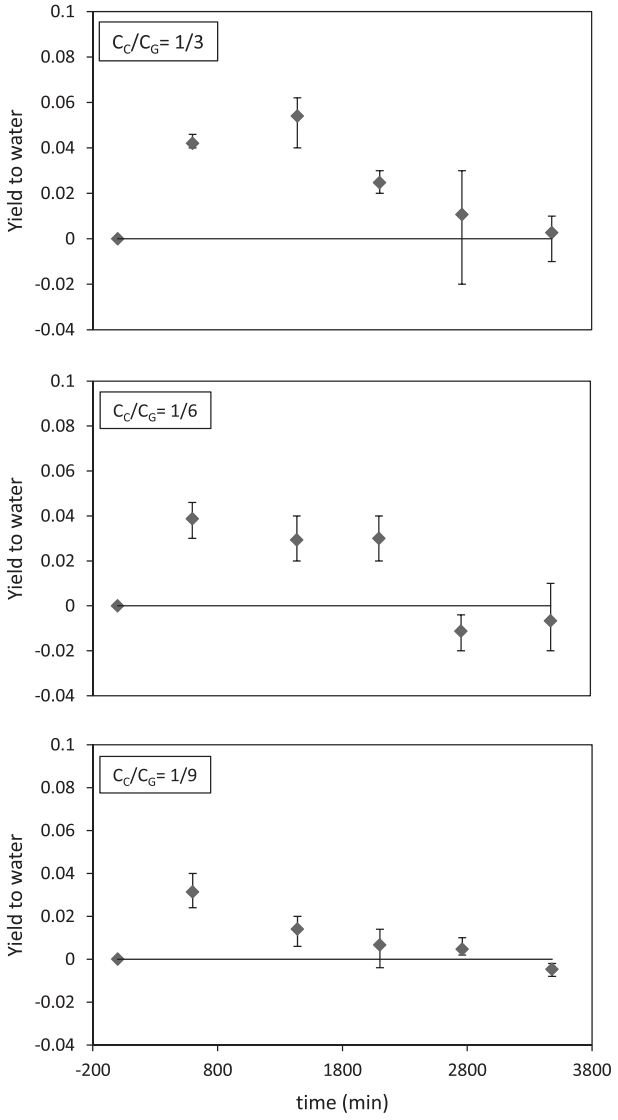


**Fig. 3.** Comparison of experimental water yield (dots) from $^1$H NMR analysis of reaction samples in DMSO and simulation data (line) using model 4 for the esterification of glycerol and cinnamic acid.

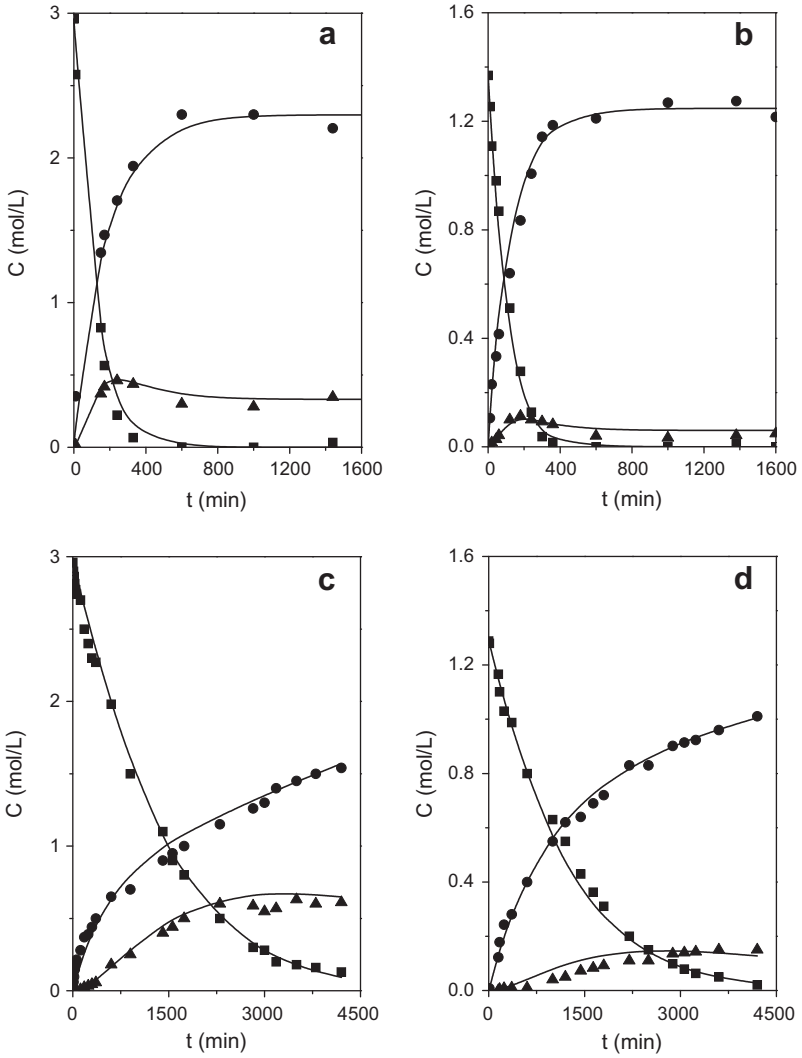


**Fig. 4.** Fitting results of the selected model to experimental data at selected conditions. ■ Cinnamic acid; ● mono-cinnamoyl glycerol; ▲ di-cinnamoyl glycerol; and – – – kinetic model fitting line. (a) $T$ = 200 °C, $C_G/C_c$ = 3/1, (b) $T$ = 200 °C, $C_G/C_c$ = 9/1, (c) $T$ = 150 °C, $C_G/C_c$ = 3/1 and (d) $T$ = 150 °C, $C_G/C_c$ = 9/1.

was controlled by an OMRON e5csv PID controller and the agitation by an IKA RW20 motor. Finally, a dry nitrogen stream is introduced, being its flow fixed by an Alicat MC/MCR series digital/analogue mass flow controller.

Solubility runs were performed by setting a temperature value between 110 and 200 °C, depending on the acid used, and mixing each acid and glycerol in a manner such that the acid/glycerol molar ratio ranged from 2/1 to 1/16. Starting from the highest concentration of the acid, glycerol was added progressively and the mixture was allowed to reach a constant absorbance at a wavelength of 650 nm in each run. When the absorbance reached values near zero, turbidity was considered negligible and the liquid mixture homogeneous; thus, in such conditions, the system was monophasic and the solubility of each acid in glycerol could be calculated.

To hinder possible oxidation side reactions, the introduction of an inert nitrogen stream into the reactor was considered, studying how to contact the nitrogen with the reacting liquid (blowing the gas into or over the liquid) as well as the nitrogen flow rate (between 0.05 and 1 L $min^{-1}$ at 200 °C and a molar ratio acid to glycerol of 1/3). To test for oxidation by-products in samples withdrawn at several reaction times and different conditions, absorbance at 420 nm was measured after dilution with the adequate quantity of ethanol. Moreover, a high value in absorbance at 275 nm is observed for UV-B filters in sunscreens [4]. Therefore, using again ethanol as a solvent, absorbance of samples at said wavelength was measured for a quick assessment of the capacity of each sample as a UV-B filter.

To ensure the presence of a single phase and further reduce the production of oxidative by-products, agitation of the reacting liquid during the esterification of cinnamic acid and glycerol was studied in a third set of preliminary runs at several stirring speeds from 200 to 1200 r.p.m. Temperature was set to 150 °C and the molar ratio of the acid to glycerol was 1/3.

During the experiments, samples were withdrawn and diluted in pure methanol to a concentration of 1 g/L. Afterwards; they were analysed using a JASCO HPLC modular system with a diode array detector (model MD 2015) at 270 nm wavelength. The esters and the acids were separated using a "Mediterranean Sea-18" column (Teknokroma) at 50 °C and a mixture of methanol: water (pH 2.2) in a volume ratio of 80:20 as eluent and a flow of 0.8 mL $min^{-1}$. Since UV–vis spectra were identical for all components, they were quantified using the ratio of their peak area and the sum of the peak areas, acting the latter as an internal standard.

### 2.2.2. Kinetic studies

Thermal esterification runs of both cinnamic and p-methoxycinnamic acids with glycerol were performed at temperature

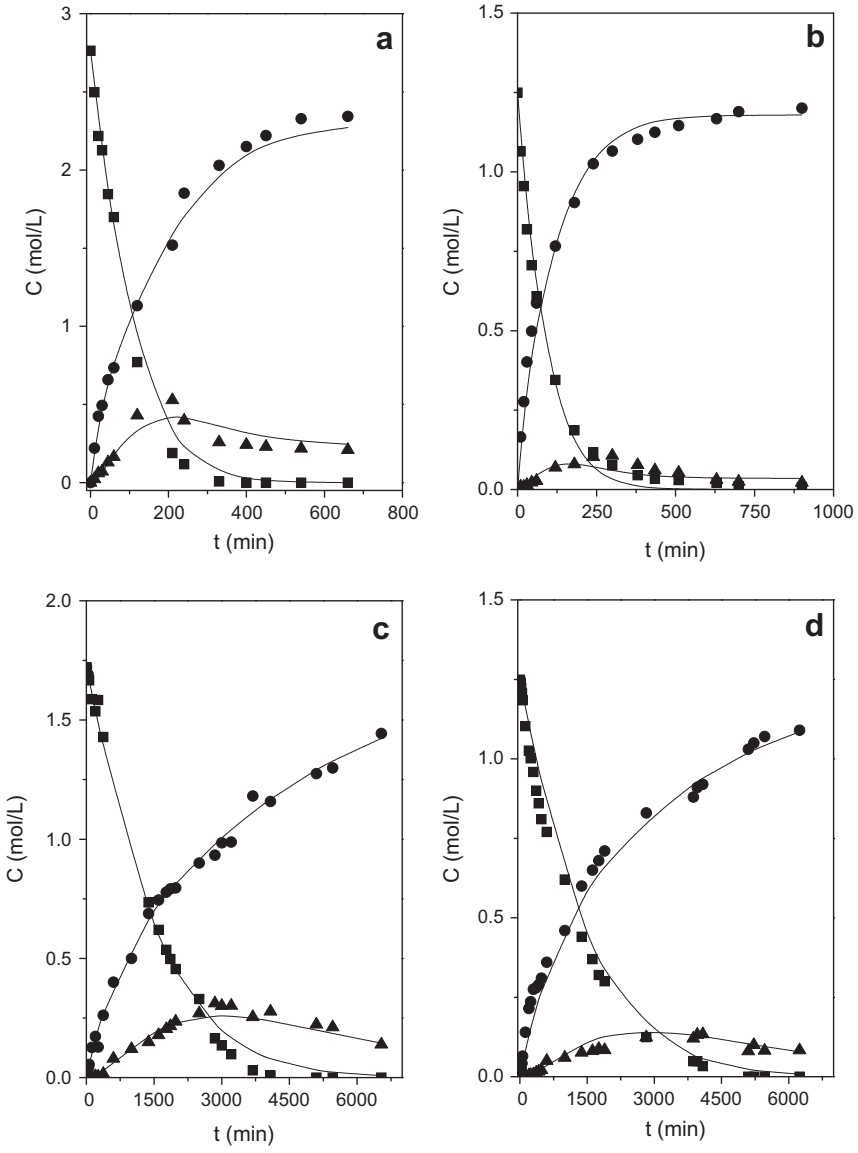


**Fig. 5.** Fitting results of the selected model to experimental data at selected conditions. ■ p-Methoxycinnamic acid; ● mono-p-methoxycinnamoyl glycerol; ▲ di-p-methoxycinnamoyl glycerol; and −−− kinetic model fitting line. (a) $T$ = 200 °C, $C_G/C_{mc}$ = 3/1, (b) $T$ = 200 °C, $C_G/C_{mc}$ = 9/1, (c) $T$ = 150 °C, $C_G/C_{mc}$ = 6/1 and (d) $T$ = 150 °C, $C_G/C_{mc}$ = 9/1.

values from 150 to 200 °C and acid/glycerol molar ratios from 1/3 to 1/9. Runs were carried out in the set-up shown in Fig. 1, flushing the liquid surface with nitrogen and stirring the reacting liquid at the conditions selected in the preliminary runs. All experimental conditions are shown in detail in Table 1. As previously described, samples were withdrawn during the runs and the aromatic compounds were analysed by RP-HPLC. In these experiments, glycerol was analysed by an HPLC technique with a refractive index detector, using citric acid as an internal standard. In this case, a REZEX ROA column for organic acids was utilised at 60 °C, employing an aqueous solution of $H_2SO_4$ 5 mM at a flow of 0.6 mL $min^{-1}$. Quantification of water was performed in triplicates in runs at 150 °C by a combination of two techniques: Karl-Fischer titration for significantly large volume samples of reacting media remaining in the reactor at the end of kinetic runs and $^1$H NMR in deuterated DMSO for the small volume samples withdrawn during runs. In the latter case, signal at $\delta$ = 3.36 was assigned to water and that at $\delta$ = 2.6 was assigned to the protons of DMSO and used as a reference peak.

*2.2.3. Mathematical methods*

The kinetic modelling was performed using the Marquard–Levenberg algorithm coupled with a fourth-order Runge–Kutta algorithm for the numerical integration of the kinetic equations, implemented in the commercial software Aspen Custom Modeler® (ACM). Several models were fitted to experimental data at a given temperature and, afterwards, to all experimental data (multivariable fitting). Model discrimination was based on physical and statistical criteria. The former implied that kinetic parameter values must be positive as well as the adequacy of the ranges of the values of the activation energies. The applied statistical criteria were the standard error for each kinetic parameter at 95% confidence, a modified version of Fischer's $F$ parameter, the residual sum of squares error (RMS error) and two information criteria: Akaike and Schwarz.

Usual statistical criteria to verify the suitability of a mathematical model are the Fischer's $F_{95}$ and the information criteria methods. Fischer's $F_{95}$ value is based on the null hypothesis that the

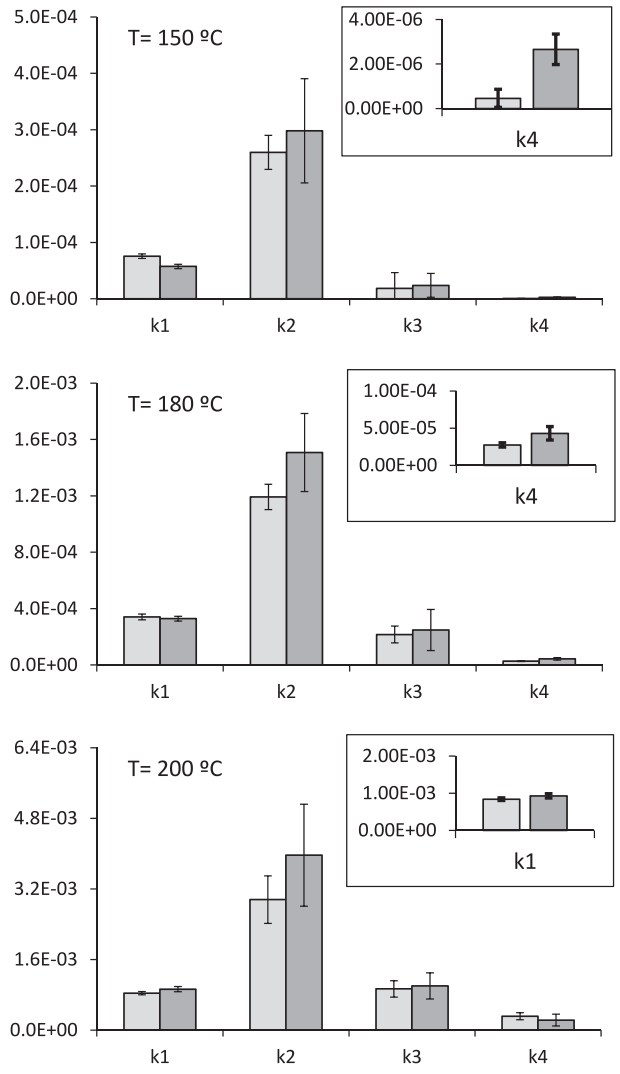


**Fig. 6.** Comparison of optimum values of constants and error intervals obtained for both acids fitting the selected models to experimental data at each temperature tested.

model fitting is successful. Considering the null hypothesis, the value of the *F* parameter must be over a certain value at a given percentage of confidence. The most common value for this confidence level is 95%, and the threshold minimum value is tabulated for the degrees of freedom in both terms in equation [1] (*K* parameters for the numerator and the difference between *N* data and *K* parameters for the denominator). Fischer's *F* value is calculated using the equation implemented in ACM:

$$F = \frac{\sum_{i=1}^{N}\left[(y_c)_i^2/K\right]}{\sum_{i=1}^{N}\left[(y_e - y_c)_i^2/(N-K)\right]} \quad (1)$$

Akaike's information criterion was developed by Hirotsugu Akaike and first published in 1974 [27]. It is a relative measurement of the goodness of fit of a statistical model. The original Akaike's information criterion (AIC) [28] was devised for very large sets of data, where the ratio of the number of data to the number of parameters is equal or higher than 40. This criterion can be calculated with the following equation:

$$AIC = N \cdot \mathrm{Ln}\left(\frac{SQR}{N}\right) + 2 \cdot K \quad (2)$$

Another criterion commonly used for the selection of the adequate statistical model for a population of data is the Schwarz criterion or Bayesian information criterion [29]. Like the information criterion introduced by Akaike, this parameter introduces a penalty to reduce over-fitting due to an excessive number of kinetic parameters in the model.

$$BIC = \mathrm{Ln}\left(\frac{SQR}{N}\right) + \frac{K}{N} \cdot \mathrm{Ln}(N) \quad (3)$$

AIC and BIC relate the number of total data with the total number of parameters, as the *F*-value calculated with equation [1] does. All these criteria penalise the use of an excessive number of parameters in the tested models. Therefore, with a similar goodness of fitting, the model with the fewest parameters will be chosen.

It is also common to use the Mean Squared Error and related criteria, such as its square root, for selecting the most statistically adequate model if all the models have the same number of parameters or to compare the goodness of fit of a given statistical model to several sets of experimental data [30]. When using ACM software, the Root Mean Squared Error is calculated by the following equation:

$$RMSE = \sqrt{\sum_{i=1}^{N}(y_e - y_c)_i^2} \quad (4)$$

## 3. Results and discussion

### 3.1. Preliminary experiments

#### 3.1.1. Solubility of cinnamic acid in glycerol

Several experiments were performed to study the solubility of cinnamic and p-methoxycinnamic acids in glycerol, varying temperature and glycerol/acid molar ratio. Runs were carried out within the range 110–200 °C and 2/1–1/16 (glycerol/acid) molar ratio; the results are reflected in Fig. 2. As shown in this figure, cinnamic acid dissolves in glycerol, reaching concentrations as high as 5 mol $L^{-1}$ (approximately, a molar ratio acid/glycerol of 1) at temperatures as low as 110 °C, so it is possible to study the synthesis of monocinnamyl glycerol in these conditions in a monophasic system with glycerol acting both as reagent and solvent. In the case of p-methoxycinnamic acid, its solubility is much lower, yet an increase in temperature involves a rapid increase of this solubility, ensuring the existence of a monophasic system for the conditions studied at temperatures slightly over 150 °C (concentration of acid near 2.8 mol $L^{-1}$, molar ratio acid to glycerol equal to 1/3). Therefore, and for both systems, the working temperature range of choice is 150–200 °C to provide a monophasic system.

#### 3.1.2. Effect of an inert atmosphere of nitrogen

Another factor to consider is the oxidation of the reaction medium, given that in preliminary runs a yellowish/brownish colour of the samples was detected. Considering that oxidation of the final product could be inconvenient for the properties of the monoester as a sunscreen ingredient, an inert atmosphere of nitrogen was considered for subsequent runs. Therefore, nitrogen flow and technique of introduction were studied to avoid or reduce the development of sample colouring (reflected in the increment of its absorbance at 420 nm) and to preserve the mixture of esters synthetized from oxidation (avoiding the reduction in sample absorbance at 275 nm).

Nitrogen was introduced by means of two different techniques, namely: bubbling it into the reacting liquid phase or flushing it over the liquid surface, thus creating a blanket of nitrogen that displaced the oxygen. Three runs were performed at 200 °C and a

molar ratio of cinnamic acid to glycerol of 1/3. The control run was performed in the absence of nitrogen. The second run was carried out introducing nitrogen at 0.2 L/min into the reacting liquid. Finally, a third run was performed blowing the nitrogen over the surface of the liquid. As Table 2 shows, conversion of the acid was lower in the absence of nitrogen and similar in the second and third runs. However, selectivity to monoester was improved when a layer of nitrogen was created over the surface of the liquid by flushing it with the gas. Spectrophotometric measurements proved that this strategy led to a lower absorbance at 420 nm (lower progress of oxidative reactions) and to a higher value in the absorbance at 275 nm (suggesting a higher potential of the final mixture as UV-B filter). As a consequence, nitrogen was introduced by flushing the surface throughout the following runs.

Once the technique of nitrogen addition was selected, gas flow rates from 0.05 to 1 L $min^{-1}$ were tested. Again, results are shown in Table 2. Apparently, an optimum for selectivity to monocinnamoyl glycerol, low selectivity to oxidation products and high preservation of UV-B filter capacity can be attained at the lowest values of flow rate tried, being 0.2 L $min^{-1}$ the best flow rate considering all of these parameters.

*3.1.3. Effect of the stirring rate*

Finally, since liquid to gas contact could be important given the oxidative side reactions, several thermal esterification runs using cinnamic acid and glycerol were carried out to select an adequate agitation rate. Runs were performed at stirring speed values of 0, 250, 500, 800, and 1200 r.p.m. at a 0.2 L $min^{-1}$ nitrogen flow rate. It should be noted that, without stirring, conversions to mono- and dicinnamoyl glycerols were lower yet very close to the results obtained with stirring. It appears that the minimal agitation caused by flushing the surface with nitrogen was sufficient and results further support the idea of the existence of a single phase in the liquid. Low stirring speed seemed to reduce, the extension of oxidation reactions as well. Therefore, the choice was a low agitation rate: 250 r.p.m.

*3.2. Kinetic model determination*

As mentioned before, to select the most adequate kinetic model for each system acid-glycerol, several runs were conducted at the conditions selected in the preliminary experiments. These runs were performed at temperatures ranging from 150 to 200 °C and acid to glycerol molar ratios from 1/3 to 1/9, for both cinnamic and methoxycinnamic acids. Samples at several reaction times were withdrawn and analysed as detailed in Section 2.2.2.

The kinetic models tested for the esterification of both acids are shown in Table 3. These models are based on the existence of esterification, hydrolysis, glycerolysis and disproportionation reactions [21,31]. Model 1 is the simplest and supposes two consecutive esterification reactions, being the first one the formation of the monoester of glycerol and the acid and the second one, its reaction with more acid to produce the diester. Model 3 is similar to model 1, adding a final reaction of the diester with glycerol to yield two molecules of monoester (therefore, a glycerolysis reaction happens). Model 5 is the most complex, featuring a disproportionation reaction where two molecules of monoester can combine to yield one of glycerol and another of diester. In every case, kinetic equations were assumed to be potential and the partial reaction order for the compounds involved was one, thus being the global order in every equation two. Models 2, 4 and 6 were derived from these three models to observe the effect of the excess of glycerol. In the latter, the partial order of glycerol is zero, supposing that a big excess of this reagent means that the temporal variation of its concentration is almost negligible. Therefore, they are pseudo-first order models. As a classical reference, Model 7 was also fitted to experimental data. This model considers esterification direct and reverse reactions: hydrolysis of the esters yielding acid and glycerol or monoester. A first order kinetic equation is also added to consider the evaporation of water due to high temperature and stripping by nitrogen. To observe this phenomenon, runs at 150 °C were performed in a modified set-up including a condensation device through which the nitrogen current flows after being in contact with the reaction liquid. In those runs, water could be condensate and removed from this nitrogen current.

The proposed kinetic models (Table 3) were fitted to all available experimental data, including concentrations of acids, esters and glycerol, according to statistical techniques described in Section 2.2.2. Table 4 reflects the statistical parameters showing the goodness of fit of each of the models to all the experimental data (at all the temperatures tested for both reaction systems for each one of the tested acids), while the kinetic parameters for the selected models for both acids feature in Table 5.

To select the best model, both physical and statistical criteria were taken into account. A first physical criterion applied was to consider the possible existence of hydrolysis reactions, as these reactions are of real importance in classical esterification processes where water concentration increases progressively. Analysis of water results shown in Fig. 3 suggest that no hydrolysis reaction takes place due to the very low concentration of this compound in the reacting liquid. Therefore, the role of water is negligible in these systems and dryness is ensured by high temperature and stripping by nitrogen. This was observed, as well, by Holser when working with refluxing toluene [24]. More to the point, if optimal values for the kinetic constants for Model 7 are used to simulate runs at 150 °C, water concentration remains always zero for both acids. Another physical criterion is the value of the activation energy, which should range between 40 and 200 kJ $mol^{-1}$ if the chemical reaction is the controlling step of the overall rate. This criterion is fulfilled by all kinetic constants in Models 1, 2, 5 and 6, for both acids. In the case of cinnamic acid, the third constant is zero and statistically meaningless. In model 7, the activation energy of the evaporation constant ranges from 25 kJ $mol^{-1}$ to 64 kJ $mol^{-1}$, depending on the acid. These values seem too high for a physical phenomenon.

As for statistical criteria, the intervals for the kinetic parameters at 95% confidence do not include zero for parameters from Models 1, 2, 5 and 6 for both acids and it is also adequate for most parameters in Models 3, 4 and 7 in both cases. Only when fitting Model 7 to cinnamic acid data, most parameters are not statistically meaningful (their interval is too wide and includes zero as a possible value for the parameter). Thus, further discrimination should be, done for Models 1, 2, 5 and 6 on the basis of information parameters, the *F* value and RMS error. The best overall fit, with the lowest RMSE value, was obtained with model 5 for both acids despite all models being good for fitting acid and glycerol concentrations. Monoester and, especially, diester concentrations are much better explained by Models 5 and 6, as shown in Table 4. All models tested have an *F*-value of 39,000 or higher, much higher than the threshold values of *F* at 95% confidence needed, which ranges from 1.844 to 2.386. Therefore, these models are statistically meaningful. However, taking into account equation [1], the *F*-value can be used to select the most adequate model on the basis of the amount of data, the number of parameters and the sum of squared residuals. In this aspect, this parameter is even better than information parameters for model selection, as it penalises over-fitting and excess of parameters more than AIC and BIC. Using *F*-value (the higher, the better), and AIC and BIC (the more negative, the better) to select among Models 1, 2, 5 and 6 leads to the selection of Model 5, being Model 6 the best one after Model 5. Therefore, model 5 is the simplest kinetic model fitted to experimental data of kinetic runs from this work, able to explain 98–99.5% of kinetic data,

depending on the compound, and esterification, glycerolysis and disproportionation reactions seem to be present in the reacting system, being hydrolysis negligible due to the absence of water. Model 6 is next in goodness of fitting due to the high excess of glycerol, such that for example, the acid concentration in reactions at an acid to glycerol molar ratio of 1/9 seems to follow a pseudo-first-order trend. The selected kinetic models fit narrowly to experimental data, as shown in Figs. 4 and 5, for both esterification processes of cinnamic and methoxycinnamic acids.

Otero et al. suggest that a combination of low acid concentration, high polyol concentration and precipitation of monoesters are reasons for monoester selectivity [21]. According to Vahteristo et al., this degree of selectivity could be explained by a combination of high rates for the esterification of the acid and the polyol and low rates for the further esterification of the monoesters, together with disproportionation reactions of the monoesters [31]. Finally, Isai et al. proved the presence of disproportionation reactions of pure monoglycerides in acid media [32]. In the reacting systems herein studied, all the reactions present, along with their respective rates, are able to explain the evolution of the concentration of diesters (diesters apparently behave as intermediate compounds, with the highest concentration values at intermediate processing time and a positive value in the long term) and the high selectivity towards monoesters, having these products maximal concentration values at the end of the reacting process. In the systems studied in this work, the excess of glycerol favours the formation of the monoesters from both acids, even though the value of the second-order reaction constant for the esterification to diesters is three to four times higher (see Fig. 6 for a comparison of absolute values of the kinetic constants with their error interval). Glycerolysis constants are three to thirty times higher than those of disproportionation, being the latter more favoured at the highest temperature. These two reactions, however, are considerably slower than the esterification reactions, so their influence is more perceived in the long term.

It can be seen, from Figs. 4 and 5 and from Table 4, that the temporal evolution of the concentrations of acid, monoester and diester are similar for both esterification processes, for cinnamic and methoxycinnamic acids, and that both kinetic models determined are similar. If the values and error intervals of the natural logarithms and activation energies of $k_3$ are compared, they overlap when the error range is taken into account. In all other cases, values are similar but statistically different. Esterification reaction rates are more influenced by temperature in the case of the p-methoxycinnamic acid than that of cinnamic acid. Disproportionation reaction rates are influenced by temperature following the opposite trend, however. Only glycerolysis reactions are identical for both reacting systems. It seems that temperature enhances more the catalytic activity of the less acidic compound, p-methoxycinnamic acid.

To delve into the comparison between the kinetic behaviour of both systems, the values of the kinetic constants obtained when fitting the models to experimental data at each temperature for both esterification processes shown in Fig. 6 can be compared. As commented in the previous paragraph, the trend of $k_1$ is slightly different in both acids, such that at low temperatures, this parameter is lower for p-methoxycinnamic acid than for cinnamic acid, while it is higher at 200 °C, including the error ranges. The overall trend is similar for $k_2$, though this constant is statistically identical for both acids. Therefore, p-methoxycinnamic acid appears to be more reactive than cinnamic acid at the highest temperatures tested in esterification reactions. The parameter related to glycerolysis ($k_3$) is identical for both acids at all the temperatures tested, reinforcing the idea that the rate of this reaction does not depend on the acid moiety. Regarding disproportionation of the monoesters ($k_4$), the kinetic constant is only similar at 200 °C, being less prone to react in this way the monoester of the cinnamic acid. As observed in the previous paragraph, the trend with temperature is opposite to that of esterification reactions: the monoester of cinnamic acid reactivity is more enhanced by this variable.

Holser et al. [4] described a process of synthesis of monoester of glycerol and cinnamic acids that consists in the catalytic esterification of glycerol with cinnamic or methoxycinnamic acid using toluene as solvent and p-toluenesulfonic acid as homogeneous catalyst to produce a possible UV filter for sunscreens, concluding that the monoester from glycerol and methoxycinnamic acid esterification has better properties to be considered as a possible UV filter. In another work, Holser [24] proposed a kinetic model for these esterification processes, consisting of two sequential irreversible first order equations for both acids, one for the formation of the monocinnamoyl glycerol, and another for the formation of the dicinnamoyl glycerol, common for both acids, cinnamic and methoxycinnamic. This model is identical to Model 2 in this work: all reactions are first-order with respect to the cinnamic species (acid or monoester) and zero-order with respect to glycerol. In this case, the temperature range is much lower (110 °C) and the concentrations of both reactants are much lower, as the reactions are performed in toluene at 110 °C (reflux) in conditions at which glycerol is soluble in this solvent. Therefore, a higher productivity ($2.013 \times 10^{-3}$ acid mol/min L, at 200 °C) is obtained due to the higher temperature and reagent concentrations.

## 4. Conclusions

Solventless esterification of glycerol with p-methoxycinnamic or with cinnamic acids in monophasic systems is possible at temperatures of 150 °C or higher at molar ratios acid to glycerol as high as 1/3. Inert gases over the reacting liquid and low agitation speeds are needed to reduce the extension of oxidation reactions.

Esterification of cinnamic acids and glycerol proceeds under these conditions following esterification reactions to monoesters and diesters of glycerol (with a residual, and negligible, presence of triesters), glycerolysis of diesters back to monoesters due to the excess of glycerol and, finally, disproportionation of monoesters to form glycerol and diesters.

Both systems herein studied present a very similar kinetic behaviour.

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