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ORIGINAL PAPER

Kinetics of Cinnamoyl Glycerol Formation

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Abstract The esterifications of glycerol with cinnamic acid, 2-methoxy cinnamic acid, and 4-methoxy cinnamic acid were investigated in batch reactions. Conversions of over 50% were achieved for cinnamic acid and 4-methoxy cinnamic acid within 8 h. After 24 h, conversions of over 80% were obtained for cinnamic acid and 4-methoxy cinnamic acid. Conversions of 33 and 40% were observed for 2-methoxy cinnamic acid after 8 and 24 h, respectively. These reactions were modeled by a system of sequential first-order rate expressions. Kinetic parameters were estimated from experimental data fit to the model equations.

Keywords Co-products · Synthesis · Ester · Reaction rates

Introduction

The current surplus of glycerol generated by the increase in fatty methyl ester production for fuel use, i.e., biodiesel, provides a versatile substrate for the synthesis of biobased products. Glycerol possesses a high degree of functionality and exhibits such favorable properties as low toxicity, low volatility, and water solubility that are suitable for the development of environmentally benign products and processes. Recent work examined the esterification of glycerol with cinnamic acid via the Mitsunobu reaction [1–3]. However, this involved the use of protecting groups to prevent the formation of unwanted products. While successful, this approach requires additional synthetic steps to block reaction sites and recover product.

Cinnamoyl esters are commonly used as organic ultraviolet (UV) filters in sunscreens and cosmetic formulations [4, 5]. Compounds such as octyl methoxycinnamate (OMC) and 2-ethylhexyl-*p*-methoxycinnamate are typical and the esters of longer chain fatty acids, hydroxy fatty acids, and epoxy fatty acids have also been prepared [6–8].

Reports have appeared concerning the risk associated with the absorption of such lipid compounds from sunscreen formulations [9–11]. The risk focuses on the bioactivity of these compounds and their potential to act as endocrine disruptors. Clinical investigations also confirmed the transdermal properties of these compounds [12, 13]. In one study with human test subjects exposed for 1 week the endocrine effects of common sunscreens were measured, however, the long-term effects of repeated applications are not known [13].

Preparation of the more hydrophilic cinnamoyl esters of glycerol were investigated as alternative UV filters with limited transdermal properties. The associated risk would be significantly reduced with such a hydrophilic compound. The reactions of glycerol with cinnamic acid, 2-methoxy cinnamic acid, and 4-methoxy cinnamic acid were studied to explore the structural and positional influence of the substituent methoxy group on reaction rate, selectivity, and conversion.

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Experimental

Materials

Glycerol (99.9%), cinnamic acid (97%), 2 methoxy cinnamic acid (98%), 4 methoxy cinnamic acid (99%), toluene (HPLC grade), and methanol (HPLC grade) were purchased from Sigma–Aldrich Chemicals, (St. Louis, MO). The catalyst *p*-toluenesulfonic acid (ptsa), 99%, was purchased from Fisher Scientific Co. (Pittsburgh, PA). All materials were used as received.

Esterification

Reactions were performed in 250-mL glass vessels fitted with a condenser and Dean Stark trap to remove the water of reaction. A magnetic stirrer bar was placed into the glass vessel and 2 g quantities of glycerol, and either cinnamic acid, 2-methoxy cinnamic acid, or 4-methoxy cinnamic acid were added. The reactants were mixed with 100 mL toluene and 100 mg ptsa catalyst while heating to reflux temperature (110 °C). The reaction mixtures were sampled periodically for the first 8 h and then after 24 h. Samples were diluted in methanol for chromatographic analysis. All reactions were replicated and analyses were performed in duplicate.

High Performance Liquid Chromatography (HPLC)

Samples were analyzed with the Agilent 1100 HPLC using a diode array detector (Agilent Technologies, Inc., Palo Alto, CA). Separations were achieved on a C18 column measuring 150 mm × 4.6 mm with 5 μm diameter packing (Alltech Associates, Inc., Deerfield, IL). Compounds were eluted from the column with isocratic methanol at 0.5 mL/min. The UV absorbance was monitored at 288 nm and spectra were obtained by scanning peaks in the range 190–400 nm. Data were collected and processed via Chemstation software (Agilent Technologies, Inc., Palo Alto, CA).

Infrared Spectra (IR)

Infrared spectra were obtained with a Thermo Nicolet, Nexus FT-IR 470 spectrometer, using the ZnSe ATR accessory. Samples, 10–20 mg, were dissolved in 2-mL volumes of diethyl ether and a drop was placed onto the ZnSe crystal. The solvent was allowed to evaporate before the spectra were collected. Spectral data were collected over the range 600–4,000 cm^{-1} and processed by Omnilab software. Strong absorbances in the 3,200–3,600 cm^{-1} region were observed for hydroxyl groups and near 1,700 cm^{-1} for ester linkages.

GC-MS

Mass spectra of silylated samples were collected using the Agilent 6890N gas chromatograph equipped with the 5973 mass selective detector operated in EI mode. Separations were achieved on the HP-5ms column, 30 m × 0.25 mm ID × 0.25 μm film thickness. Helium was used as the carrier gas with a linear velocity of 35 cm/s. The oven temperature was programmed from 120 to 240 °C at 10 °C/min with an initial 2 min hold and a final 10 min hold. The inlet was heated to 230 °C and set for splitless injections with a 1 μL injection volume. The detector source was heated to 230 °C and the detector quadrupole was heated to 150 °C. Data were collected and processed via Chemstation software.

Molecular Modeling

Solubility parameters were calculated using Molecular Modeling Pro, Norgwyn Montgomery Software, Inc., North Wales, PA.

Results and Discussion

The reaction of glycerol with cinnamic acid, 2-methoxy cinnamic acid, and 4-methoxy cinnamic acid proceeded at reflux conditions. Products were characterized by FTIR and GC-MS. The infrared spectra displayed a strong absorbance at 1,700 cm^{-1} which indicated the presence of the ester function. The shift from a more typical absorbance at 1,740 cm^{-1} is attributed to the double bond conjugated with the aromatic ring structure. A pair of strong sharp bands was observed at 1,172 and 1,116 cm^{-1} consistent with the C–O stretching mode. Analysis by GC-MS identified the molecular ions of the monoester and diester products. The location of the ester linkages at the primary alcohol sites of glycerol were determined from the fragmentation pattern of the trimethyl silyl derivatives [14].

The progress of the reaction was followed by the disappearance of the acid and the formation of products. This was easily measured by the strong UV absorbance of the aromatic group. Plots of concentration versus time are shown for the esterification of cinnamic acid and glycerol in Fig. 1. The monoester was produced rapidly in the first 3 h before the appearance of the diester product. After 8 h of reaction time the cinnamic acid has decreased to 41.9% of the starting

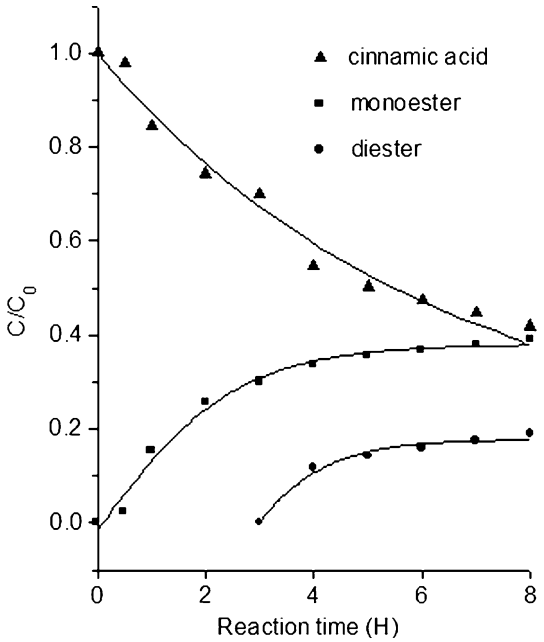

Fig. 1 Concentration versus time plot for the reaction of cinnamic acid and glycerol

concentration with production of 39.1% of the monoester and 19% of the diester. Formation of the 4-methoxy and the 2-methoxy cinnamoyl glycerol esters followed similar trends with the 4-methoxy cinnamic acid decreasing to 47.5% and the 2-methoxy cinnamic acid decreasing to 67.5% of their initial concentrations (Figs. 2, 3).

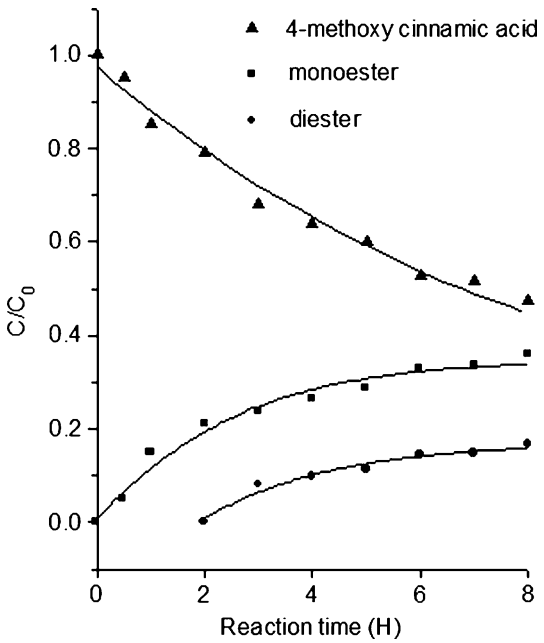

Fig. 2 Concentration versus time plot for the reaction of 4-methoxy cinnamic acid and glycerol

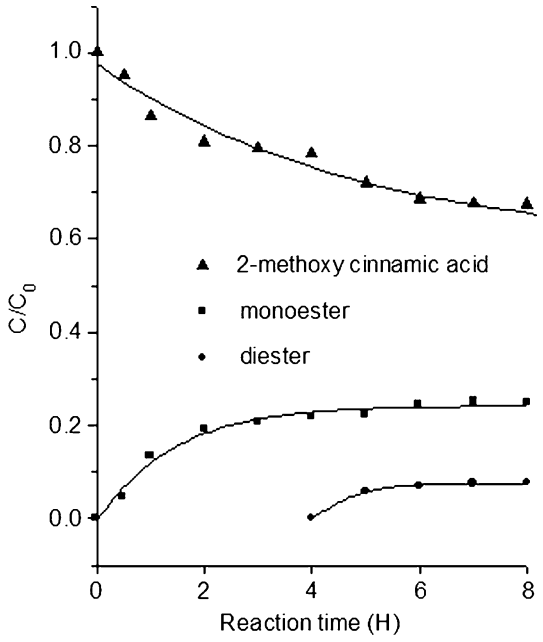

Fig. 3 Concentration versus time plot for the reaction of 2-methoxy cinnamic acid and glycerol

The composition of the reaction mixtures after 8 and 24 h are compared in Table 1. Conversions of 82.8% for cinnamic acid and 88.1% for 4-methoxy cinnamic acid were obtained after 24 h. The conversion of 2-methoxy cinnamic acid was 40% after 24 h. The yields of the ester products are tabulated with the corresponding acid. In all cases the yields of monoesters exceeded those of the diesters which indicated that the reaction rates for the formation of the monoesters was greater than the rates for the diesters. Selectivities for the monoesters ranged from 2.1 for the 4-methoxy cinnamic acid esters to 3.2 for the 2-methoxy cinnamic acid esters after 8 h compared to 1.1 and 2.5, respectively, after 24 h.

Based on these results it appears possible to obtain the monoester product in nearly 100% yield by performing the reaction in a continuous flow reactor system. In this way

Table 1 Composition of reaction mixtures after 8 and 24 h at reflux

Compound	8 h (%)	24 h (%)
Cinnamic acid	41.9	17.2
Monoester	39.1	45.1
Diester	19.0	37.7
4-Methoxy cinnamic acid	47.5	11.9
Monoester	35.8	46.7
Diester	16.7	41.4
2-Methoxy cinnamic acid	67.5	60
Monoester	24.8	28.5
Diester	7.7	11.5

Table 2 Equations used to model the sequential reaction of cinnamic acid with glycerol

Reaction 1: monoester	Cinnamic acid + glycerol → cinnamoyl glycerol + water
Rate expression 1	d/d*t* [cinnamoyl glycerol] = K1*[cinnamic acid]
Reaction 2: diester	Cinnamic acid + cinnamoyl glycerol → dicinnamoyl glycerol + water
Rate expression 2	d/d*t* [dicinnamoyl glycerol] = K2*[cinnamoyl glycerol]
Combined rate expression	−d/d*t* [cinnamic acid] = d/d*t* [cinnamoyl glycerol] + d/d*t* [dicinnamoyl glycerol]
	or
	−d/d*t* [cinnamic acid] = K1* [cinnamic acid] + K2*[cinnamoyl glycerol]

Square brackets denote compound concentrations, K1 and K2 are the first-order rate constants, and the time derivative operator is represented by d/d*t*

Table 3 Rate constants determined by fitting experimental data to sequential first-order irreversible model equations

	K1 (h-1)	K2 (h-1)	*r*	*P*
Cinnamic acid	0.1286	0.0499	0.9760	0.0231
4-Methoxy cinnamic acid	0.1219	0.0583	0.9778	0.0221
2-Methoxy cinnamic acid	0.0610	0.0266	0.9776	0.0223

the monoester may be removed from the product stream before the formation of the diester. The appropriate continuous flow reactor system for the production of cinnamoyl glycerol would have a residence time of less than 3 h. The same strategy could be applied for the reactions of the 2- methoxy and 4-methoxy cinnamoyl glycerol esters using residence times of less than 4 and 2 h, respectively. For efficient operation in this continuous mode the solvent would be recycled to the reactor after product recovery.

The kinetics of these sequential esterification reactions were modeled by a series of first-order irreversible rate expressions (Table 2). Experimental data were fit to the model equations by a least squares technique to obtain values of the rate constants. These results are listed in Table 3. The rate of monoester formation, K1, was more than twice the rate of diester formation, K2, for all the reactions studied. The rate of conversion of cinnamic acid to the monoester was the most rapid. The rate of conversion of 4-methoxy cinnamic acid was only slightly slower while 2-methoxy cinnamic acid exhibited the slowest rate. The rate of diester formation from cinnamic acid and 4-methoxy cinnamic acid were similar while 2-methoxy cinnamic acid again exhibited the slowest rate. The differences in the reaction rates observed between the 2- methoxy and 4-methoxy cinnamic acids are attributed to the position of the methoxy group on the aromatic ring of the cinnamic acid. This was interpreted to be due predominately to conformational effects. The proximity of the methoxy group to the side chain containing both the unsaturated bond and the carboxylic acid function is reduced when the methoxy group is attached at the *para* position compared to the *ortho* position.

The UV spectra of cinnamic acid, 2-methoxy cinnamic acid, and 4-methoxy cinnamic acid are shown in Fig 4. The spectra of the esters exhibit the same absorbance characteristics as the acids from which they are derived. However, the spectra of the acids display significant differences. The absorbance spectra of 2-methoxy cinnamic acid and 4-methoxy cinnamic acid extend to 350 nm compared to 315 nm for cinnamic acid. Materials absorbing at the longer wave lengths are more useful as UV filters [11]. These methoxy cinnamoyl glycerol esters also possess more hydrophilic character than cinnamoyl esters prepared from fatty compounds such as vegetable seed oils and offer potential for use in personal care products as UV filters where minimal transdermal properties are required. Solubility parameters were calculated for the monoester

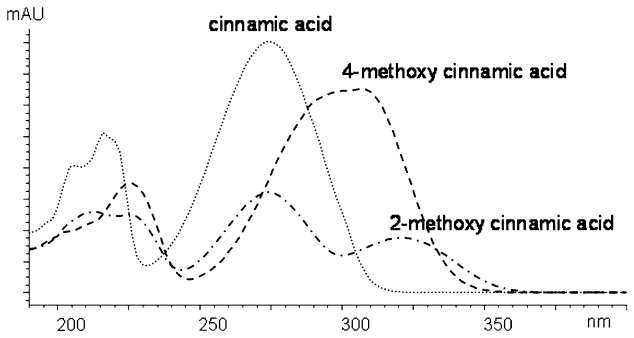

Fig. 4 UV spectra of cinnamic acid, 2-methoxy cinnamic acid, and 4-methoxy cinnamic acid

Table 4 Calculated solubility parameters for 4-methoxy cinnamoyl glycerol and cinnamoyl stearoyl glycerol

Compound[a]	4mCG	D4mCG	CSG
Log KOW[b]	0.354711	0.76598	5.9949
Hydrophilic/lipophilic balance[c]	10.8524	7.78674	4.3652

[a] 4mCG: 4-methoxy cinnamoyl glycerol; D4mCG: 1, 3-di-4-methoxy cinnamoyl glycerol; CSG: 1-cinnamoyl, 3-stearoyl glycerol

[b] Log octanol/water partition coefficient using modified Hansch fragments

[c] Calculated by Griffin's method

and diester products of 4-methoxy cinnamic acid with glycerol using molecular modeling techniques. These results are presented in Table 4 and compared to values calculated for the diester compound formed from glycerol with cinnamic acid and stearic acid. The log of the octanol/water partition coefficient shows an increasing trend as glycerol is derivatized with increasingly lipophilic substituents. A similar shift towards lipophilic behavior is seen in the decreasing values of the hydrophilic/lipophilic balance (HLB). This solubility behavior can be significant in formulations where a UV filter is needed but a strongly lipophilic compound would either not be compatible with other ingredients or otherwise problematic.

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References

1. Mitsunobu O (1981) The use of diethyl azodicarboxylate and triphenylphosphine in synthesis and transformation of natural products. Synthesis 1:1–28
2. Hughes DL, Reamer RA, Bergan JJ, Grabowski EJJ (1988) A mechanistic study of the Mitsunobu esterification reaction. J Am Chem Soc 110:6487–6491
3. Batovska DI, Kishimoto T, Bankova VS, Kamenarska ZG, Ubukata M (2005) Synthesis of some phenylpropenoid monoglycerides via the Mitsunoba protocol. Molecules 10:552–558
4. Freitas ZMF, Goncalves JCS, Santos EP, Verganini A (2001) Glyceridic esters of *p*-methoxycinnamic acid. A new sunscreen of the cinnamate class. Int J Cosmet Sci 23:147–152
5. Freitas ZMF, Goncalves JCS, Santos EP, Verganini A (2005) Glyceridic esters of *p*-methoxycinnamic acid. A new sunscreen of the cinnamate class. Eur J Pharm Sci 25:67–72
6. Compton D, Laszlo JA, Berhow MA (2000) Synthesis of ferulate esters. J Am Oil Chem Soc 77:513–519
7. Compton DL, Laszlo JA, Isabell TA (2004) Cinnamoyl esters of lesquerella and castor oil: novel sunscreen active ingredients. J Am Oil Chem Soc 81:945–951
8. Esen H, Kusefoglu SH (2003) Photolytic and free-radical polymerization of cinnamate esters of epoxidized plant oil triglycerides. J Appl Polym Sci 89:3882–3888
9. Benson HA (2000) Assessment and clinical implications of absorption of sunscreens across skin. Am J Clin Dermatol 1:217–224
10. Freitas ZMF, Machado GM, Dellamora-Oritz GM, Santos EP, Goncalves JCS (2000) Evaluation of phototoxicity of different sunscreens: 1,2,3-propanetriol-1,3-dipalmitoyl-2-*p*-methoxycinnamoyl and 1,2,3-propanetriol-1,3-dioctanoyl-2-*p*-methoxycinnamoyl. STP Pharma Sci 10:239–242
11. Nohynek GJ, Schaefer H (2001) Benefit and risk of organic ultraviolet filters. Reg Tox Pharma 33:285–299
12. Chatelain E, Gabard B, Surber C (2003) Skin penetration and sun protection factor of five UV filters: effect of the vehicle. Skin Phamacol Appl Skin Physiol 16:28–35
13. Janjua NR, Mogensen B, Andersson AM, Petersen JH, Henriksen M, Skakkebaek NE, Wulf HC (2004) Systemic absorption of the sunscreens benzophenone-2, octyl-methoxycinnamate, and 3-(4-methyl-benzylidene) camphor after whole-body topical application and reproductive hormone levels in humans. J Invest Dermatol 123:57–61
14. Graca J, Pereira H (2000) Suberin structure in potato periderm: glycerol, long-chain monomers, and glyceryl and feruloyl dimers. J Agric Food Chem 48:5476–5483