Solubilities of Cinnamic Acid Esters in Organic Solvents

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The solubilities of three cinnamic acid esters, namely, methyl ferulate, methyl *p*-coumarate, and methyl sinapate, have been measured in *tert*-butanol, *tert*-pentanol, ethyl acetate, and *n*-hexane, at the temperature range of (303.15 to 321.15) K. It is shown that *tert*-pentanol is the best solvent for methyl *p*-coumarate and methyl ferulate and ethyl acetate for methyl sinapate, while the nonpolar *n*-hexane is the worst solvent. Using the experimentally measured solubilities, the thermodynamic properties of dissolution of the three esters have been calculated. To better understand the solubilization process, the melting temperatures and the enthalpies of fusion of the three esters were determined by differential scanning calorimetry. Finally, successful correlation of the experimental data was achieved with the UNIQUAC and the nonrandom two-liquid (NRTL) activity coefficient models.

Introduction

Antioxidants are compounds whose presence in small quantities can retard or even cease the oxidation process in autoxidable materials. This feature makes antioxidants particularly important for many applications involving mainly the food and drug industry, while other important uses of antioxidants can also be found in the manufacture of lubricants,[1] plastics,[2] and cosmetics.[3]

Natural antioxidants from dietary sources include, among others, phenolic compounds such as phenolic acids.[4] Phenolic acids, including hydroxylated (*p*-coumaric acid, caffeic acid) or methoxylated (ferulic acid) derivatives of cinnamic acids, are natural components of the plant cell wall (widely present in cereals and legumes) that are covalently linked to polysaccharides through ester linkages.[5] It is well-recognized that cinnamic acid derivatives exhibit antioxidative activity, peroxy radical scavenging activity, and they are inhibitors of carcinogenesis.[6] Moreover, esters of various cinnamic acids isolated from plants are pharmacologically active compounds known to have antimicrobial and/or antiviral activity[7] and also the potential to be used in the formulation of antimicrobial, antiviral, and/or anti-inflammatory agents.[8−10] The biological activities of these compounds are influenced not only by their structural features but also by their degree of lipophilicity.[11,12] The modification of lipophilization of cinnamic acids via their acylation can be used as a tool to produce derivatives with increased lipophilicity and antioxidant potency. Furthermore, the lipophilization of these natural compounds can enhance their solubility and miscibility in oil-based formulas and emulsions and thus can be used as effective antioxidants in multiphase food products and pharmaceuticals.[13]

To design and optimize chemical processes for the production of cinnamic acid derivatives, for example, enzymatic acylation reactions, or separation processes for their recovery, such as crystallization or liquid extraction, suitable solvents have to be selected. The successful completion of such task requires the knowledge of reliable phase equilibrium data. In the case of cinnamic acids, solubility data of ferulic, caffeic, *trans*-cinnamic, and *o*-coumaric acid in water[14,15] and in some chloride salts aqueous solutions[16] have been reported. Also, Trimble[17] presented the solubility of cinnamic acid in furfural at three temperatures. However, in the case of cinnamic acid esters (CAEs), to the best of our knowledge, no solubility data in organic solvents have been presented in the literature so far.

This work focuses on the solubilities of three CAEs, namely, methyl *p*-coumarate (MpCA), methyl ferulate (MFA), and methyl sinapate (MSA), in four organic solvents, which are widely used in the food industry as well as for biotechnological applications: *tert*-butanol, *tert*-pentanol, ethyl acetate, and *n*-hexane. This study is a continuation of a previous work[18] concerning the solubility measurements of the CAEs in ionic liquids (ILs), which aims to compare these two classes of solvents in terms of their solvating capacity for CAEs. Furthermore, the melting point temperatures and the enthalpies of fusion of the CAEs were determined by differential scanning calorimetry (DSC). The thermodynamic properties of dissolution have also been estimated by utilizing the experimentally measured solubilities. Finally, the experimental solubilities have been modeled with the UNIQUAC and nonrandom two-liquid (NRTL) equations.

Experimental Section

Materials. Methyl *p*-coumarate (MpCA, purity in mass fraction is greater than 98 %, CAS no. 3943-97-3), methyl ferulate (MFA, purity in mass fraction is greater than 98 %, CAS no. 2309-07-1), and methyl sinapate (MSA, purity in mass fraction is 98.5 %, CAS no. 20733-94-2) were obtained from Apin Chemicals. Their chemical structures are presented in Table 1. Methanol, acetonitrile, and water, all HPLC grade, were obtained from SDS-Carlo Erba Reactifs, France, acetic acid (pro analysis) from Merck, *tert*-butanol (purity in mass fraction is 99.5 %) from Acros Organics, *tert*-pentanol (purity in mass fraction is 99 %) from Aldrich, and ethyl acetate (HPLC) and *n*-hexane (purity in mass fraction is 95 %) from Labscan. *tert*-Butanol and *tert*-pentanol were dried before use over molecular

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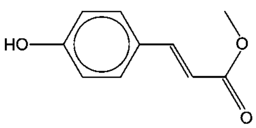
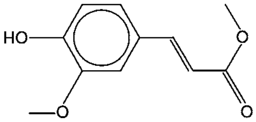
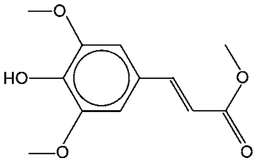
Table 1. Names, Structures, and Abbreviations of Names of the Three CAEs Presented in This Study

Name	Structure	Abbreviation
methyl *p*-coumarate		MpCA
methyl ferulate		MFA
methyl sinapate		MSA

sieves (3 Å) for at least one week. The rest of the materials were used as obtained.

Solubility Measurements

Apparatus. The equilibrium runs were performed in a Thermomixer Comfort (Eppendorf). This apparatus combines stirring up to 1400 r·min^{-1} and heating (up to 372.15 K) or cooling (13 K below room temperature). The accompanied thermoblock can accommodate 24 micro test tubes for 2 mL volumes. The temperature readings of the thermomixer have been checked using an external thermometer, which was calibrated with the Isocal-6 Venus$^{\mathrm{Plus}}$ 2140 calibrator of temperature sensors.

Procedure. At least 200 μL of each solvent was placed in the 2 mL volume safe-lock micro test tube. An excess quantity of each methyl ester was then added. At constant temperature, measured with an uncertainty of ± 0.2 K, the solutions were stirred at 1400 r·min^{-1} for 24 h. Solution samples, on the order of (10 to 20) μL, were then withdrawn using adjustable micropipets. The sampling tips of the pipettes were preheated at the temperature of the experiment to avoid solid precipitation. Before sampling, each solution was centrifuged for 30 s to ensure that no precipitated solute was drawn during sampling. All experiments were performed at least in duplicate.

Analysis. All samples were analyzed by reverse phase high-performance liquid chromatography (HPLC). The HPLC system was equipped with a Jusco PU-1580 pump, an ICI LC 1200 UV−vis detector set at 280 nm, and a BDS Hypersil C18 column ((250 × 4.6) mm^2, particle size 5 μm, Thermo Scientific). The eluent solution used was a mixture of acetonitrile/water (80/20 v/v) with 0.1 % acetic acid. The flow rate was adjusted at 1 mL·min^{-1}, and the column temperature was kept constant at 303.15 K. The injection volume was 50 μL. The eluent solution was degassed with helium.

DSC Measurements

Procedure. Thermograms of the CAEs were obtained using a differential scanning calorimeter DSC 6 (Perkin-Elmer). Samples of (20 to 26) mg (weighed at a precision of ± 0.1 mg on a Kern analytical balance) were hermetically sealed into aluminum crucibles and heated under a nitrogen stream in the measuring cell, while an empty crucible was used as a reference. Runs were performed with a 10 K·min^{-1} heating rate in the temperature range of (293.15 to 433.15) K for

Table 2. Average Melting Temperature (T_m) and Molar Enthalpy of Fusion ($\Delta_{fus}H$) of Methyl *p*-Coumarate, Methyl Ferulate, and Methyl Sinapate

	T_m / K		$\Delta_{fus}H$ / J·mol^{-1}	
compound	this work	literature	this work	literature
methyl *p*-coumarate	410.71 ± 0.52	410.15,[22,23] 409.15[24]	30216 ± 882	NA
methyl ferulate	335.71 ± 0.44	336.15 to 337.15[22]	25836 ± 923	NA
methyl sinapate	361.79 ± 0.55	365.15 to 366.15[25]	29858 ± 1379	NA

Table 3. Mole Fraction Solubilities (x) of Methyl *p*-Coumarate, Methyl Ferulate, and Methyl Sinapate in Different Solvents at T = (303.15 to 321.15) K

	T	methyl *p*-coumarate		methyl ferulate		methyl sinapate	
solvent	K	x	± SD	x	± SD	x	± SD
t-butanol	303.15	0.0977	0.0015	0.1821	0.0017	0.0184	0.0007
	307.15	0.1129	0.0020	0.2086	0.0028	0.0234	0.0010
	312.15	0.1278	0.0032	0.2474	0.0035	0.0523	0.0020
	317.15	0.1429	0.0038	0.2946	0.0055	0.0743	0.0033
	321.15	0.1711	0.0050	0.3248	0.0080	0.0973	0.0051
t-pentanol	303.15	0.1156	0.0003	0.2153	0.0001	0.0264	0.0005
	307.15	0.1260	0.0019	0.2457	0.0020	0.0336	0.0015
	312.15	0.1543	0.0023	0.2870	0.0030	0.0644	0.0035
	317.15	0.1744	0.0029	0.3120	0.0039	0.0926	0.0039
	321.15	0.2005	0.0040	0.3421	0.0056	0.1397	0.0044
ethyl acetate	303.15	0.0856	0.0012	0.2172	0.0015	0.1169	0.0023
	307.15	0.0915	0.0013	0.2468	0.0049	0.1276	0.0021
	312.15	0.0997	0.0025	0.2792	0.0050	0.1466	0.0026
	317.15	0.1082	0.0030	0.3049	0.0096	0.1569	0.0030
	321.15	0.1130	0.0040	0.3339	0.0033	0.1678	0.0040
n-hexane	303.15	$2.81\cdot10^{-05}$	$2\cdot10^{-07}$	$1.12\cdot10^{-03}$	$4\cdot10^{-05}$	$2.92\cdot10^{-04}$	$4\cdot10^{-06}$
	307.15	$4.38\cdot10^{-05}$	$1.1\cdot10^{-06}$	$2.11\cdot10^{-03}$	$6\cdot10^{-05}$	$3.83\cdot10^{-04}$	$1.0\cdot10^{-05}$
	312.15	$6.18\cdot10^{-05}$	$1.7\cdot10^{-06}$	$2.51\cdot10^{-03}$	$1.5\cdot10^{-04}$	$4.95\cdot10^{-04}$	$1.2\cdot10^{-05}$
	317.15	$8.13\cdot10^{-05}$	$3.1\cdot10^{-06}$	$3.54\cdot10^{-03}$	$1.4\cdot10^{-04}$	$7.43\cdot10^{-04}$	$3.0\cdot10^{-05}$
	321.15	$1.24\cdot10^{-04}$	$5\cdot10^{-06}$	$4.16\cdot10^{-03}$	$2.5\cdot10^{-04}$	$8.04\cdot10^{-04}$	$5.4\cdot10^{-05}$

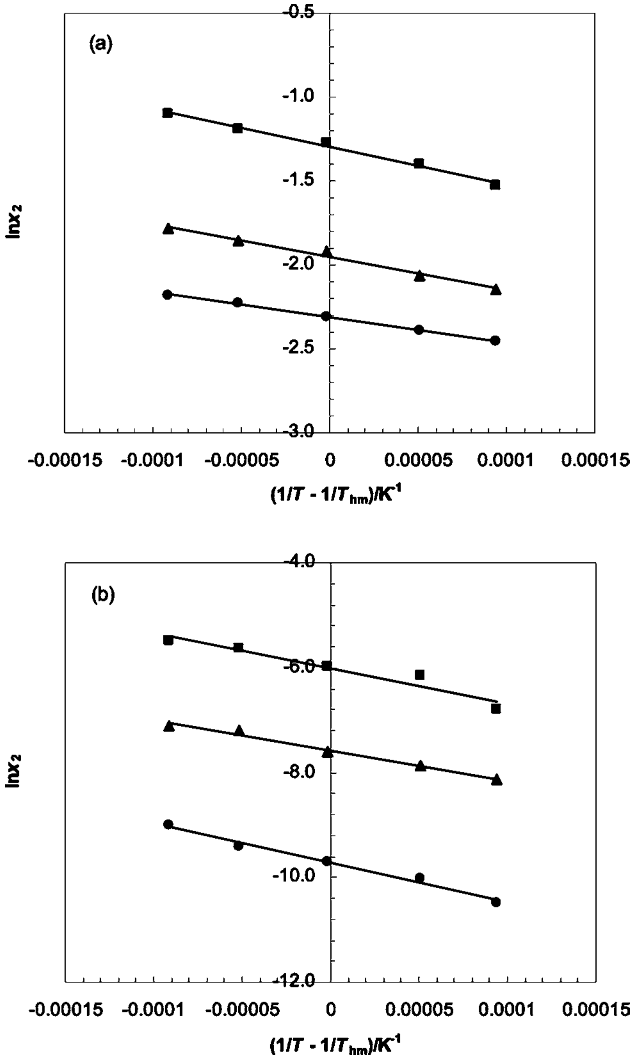


Figure 1. Temperature dependency of the solubility x of: ●, methyl *p*-coumarate; ▲, methyl sinapate; and ■, methyl ferulate in (a) ethyl acetate and (b) *n*-hexane.

MpCA, (293.15 to 373.15) K for MFA, and (293.15 to 453.15) K for MSA. All crucibles were weighed before and after DSC measurements so as to check for mass loss. When mass loss was higher than 1 %, the results were rejected. All experiments were performed at least four times.

Thermodynamic Properties of Dissolution

Using the van't Hoff analysis, the thermodynamic properties of dissolution, namely, the molar Gibbs energy ($\Delta_{sol}G^o$), enthalpy ($\Delta_{sol}H^o$), and entropy ($\Delta_{sol}S^o$) of dissolution, can be calculated by utilizing the experimental solubility data. These thermodynamic properties reflect the change of the solution properties due to the presence of the solute at its infinite dilution, at a given temperature. Assuming that the activity coefficient of the solute is equal to 1 in the hypothetical dilute ideal solution and using the Krug et al.[19] approach, the following modified van't Hoff expression is obtained

$$\left[\frac{\partial \ln x_2}{\partial\left(\frac{1}{T} - \frac{1}{T_{hm}}\right)}\right]_P = -\frac{\Delta_{soln}H^o}{R} \tag{1}$$

In eq 1, x_2 is the mole fraction solubility of the solute, R the ideal gas constant, P the pressure, and T_{hm} the harmonic mean of the experimental temperatures, which is calculated as

$$T_{hm} = \frac{n}{\sum_{i=1}^{n} \frac{1}{T_i}} \tag{2}$$

where n is the number of temperatures studied. In the present study, T_{hm} is equal to 312 K. With application of linear regression models, $\Delta_{soln}H^o$ values can be calculated.

Following the approach proposed by Krug et al., the molar Gibbs energy change for the solution process ($\Delta_{soln}G^o$) is calculated at T_{hm} by

$$\Delta_{soln}G^o = -RT_{hm}K \tag{3}$$

where K is the intercept obtained in the linear regression analysis of $\ln x_2$ versus ($1/T - 1/T_{hm}$). Finally, the molar entropy change for the solution process ($\Delta_{soln}S^o$) is obtained from

$$\Delta_{soln}S^o = \frac{\Delta_{soln}H^o - \Delta_{soln}G^o}{T_{hm}} \tag{4}$$

Thermodynamic Modeling

By neglecting the terms that account for the difference between the heat capacity of the solid and that of the subcooled liquid at the corresponding temperature, the mole fraction solubility, x_2, of the solute in a solvent is calculated by the following equation

$$\ln x_2 = -\ln \gamma_2 - \frac{\Delta_{fus}H(T_m)}{RT}\left[1 - \frac{T}{T_m}\right] \tag{5}$$

where γ_2, $\Delta_{fus}H$, and T_m stand for the activity coefficient, the enthalpy of fusion, and the melting temperature of the solid solute.

In this study, two local composition activity coefficient models were used to correlate the solubility data, the NRTL[20] and UNIQUAC.[21] For each model, two temperature-independent interaction parameters were determined, per the binary CAE/solvent system, by minimizing the following objective function (OF)

$$\mathrm{OF} = \sqrt{\frac{\sum_{i}^{n}\left(\frac{x_2\gamma_{2,calcd}}{x_2\gamma_2} - 1\right)^2}{\mathrm{NP}}} \tag{6}$$

where NP is the number of experimental points, x_2 and γ_2 are the experimental solubility and the corresponding activity coefficient values, and $\gamma_{2,calcd}$ is the activity coefficient calculated with the NRTL or UNIQUAC equation at x equal to x_2.

Results and Discussion

Table 2 presents the melting properties of the studied compounds, along with literature values of the melting point temperatures. Very good agreement is observed between our results and the literature data for MpCA and MFA, while a difference of about 4 K is observed for MSA. However, it should be noted that the purity of MSA is not given in the work of Sanz and Marco[25] and that the T_m value measured with a Reichert apparatus has not been corrected. MFA has a lower melting point and heat of fusion than MpCA; that is, the addition of a methoxy group in the aromatic ring decreases the melting properties. On the other hand, MSA has a higher melting point and heat of fusion than MFA; that is, the addition of a second methoxy group increases the melting properties. A similar behavior is also observed in the melting point temperatures of

Table 4. Thermodynamic Properties of Dissolution of Methyl *p*-Coumarate, Methyl Ferulate, and Methyl Sinapate in Different Organic Solvents and Corresponding Standard Deviations

solvent	$\Delta_{\mathrm{soln}}G^{\mathrm{o}}$ / kJ·mol^{-1}	SD	$\Delta_{\mathrm{soln}}H^{\mathrm{o}}$ / kJ·mol^{-1}	SD	$\Delta_{\mathrm{soln}}S^{\mathrm{o}}$ / J·mol^{-1}·K^{-1}	SD
			Methyl *p*-Coumarate			
t-butanol	5.33	0.02	23.7	0.84	59.0	2.63
t-pentanol	4.90	0.01	25.1	0.63	64.8	1.99
ethyl acetate	6.00	0.00	12.8	0.20	21.7	0.64
n-hexane	25.2	0.04	62.9	2.08	120.8	6.53
			Methyl Ferulate			
t-butanol	3.64	0.01	26.5	0.32	73.2	1.01
t-pentanol	3.33	0.01	20.5	0.67	55.0	2.10
ethyl acetate	3.37	0.01	18.8	0.48	49.6	1.52
n-hexane	15.6	0.09	55.2	4.14	126.9	13.0
			Methyl Sinapate			
t-butanol	8.11	0.08	79.3	3.74	228.2	11.7
t-pentanol	7.32	0.05	76.5	2.21	221.9	6.94
ethyl acetate	5.06	0.01	16.4	0.55	36.3	1.71
n-hexane	19.7	0.04	47.5	1.77	89.2	5.56

Table 5. Interaction Parameters for NRTL and UNIQUAC Models and Respective Average Relative Deviations for the Solubility of CAE (2) in the Organic Solvent (1)

	NRTL[a]			UNIQUAC[b]		
solvent	$\Delta g_{12}/R$ / K	$\Delta g_{21}/R$ / K	ARD[c] / %	$\Delta u_{12}/R$ / K	$\Delta u_{21}/R$ / K	ARD[c] / %
			Methyl *p*-Coumarate			
t-butanol	1607.8	−922.03	2.1	−190.11	144.71	2.1
t-pentanol	2005.8	−977.63	2.2	−198.19	139.16	3.0
ethyl acetate	−638.57	3195.2	3.5	−355.71	1872.4	0.5
n-hexane	2172.6	−17.95	9.6	408.00	−3.450	9.7
			Methyl Ferulate			
t-butanol	−315.27	1167.7	2.0	−229.11	539.51	1.6
t-pentanol	−445.68	2000.7	1.7	−260.71	648.68	2.1
ethyl acetate	−161.27	4150.8	1.3	−262.91	761.61	1.8
n-hexane	2570	−593.21	11.1	462.00	−143.60	12.2
			Methyl Sinapate			
t-butanol	1339.8	−504.60	21.6	273.04	−145.69	20.2
t-pentanol	1454.2	−561.91	11.3	361.14	−194.83	8.1
ethyl acetate	−372.09	3110.4	3.3	−274.41	795.39	1.4
n-hexane	2203.6	−267.81	3.0	337.75	−53.424	2.9

[a] Nonrandomness parameter of the NRTL model was set equal to 0.2. [b] The van der Waals volume (R) and van der Waals area (Q) parameters were calculated from the UNIFAC tables.[29] MpCA: $R = 6.7834$, $Q = 5.315$; MFA: $R = 7.7623$, $Q = 6.123$; MSA: $R = 8.7412$, $Q = 6.931$, respectively. [c] $\mathrm{ARD} = 1/5(\sum_{i=1}^{5}(|x_{\mathrm{exptl}} - x_{\mathrm{calcd}}|)/x_{\mathrm{exptl}})$.

phenol ($T_m = 314.15$ K),[26] 2-methoxyphenol ($T_m = 301.15$ K),[27] and 2,6-dimethoxyphenol ($T_m =$ (323.15 to 330.15) K).[28]

Table 3 presents the solubilities of the three CAEs in the various organic solvents and temperatures. Each solubility value reported is an average of at least two independent experiments. The corresponding standard deviation (SD) for each mean value is also given. By applying linear regression models on the modified van't Hoff plots of the experimental solubilities, typical examples are shown in Figure 1, and the thermodynamic properties of the dissolution process of the three esters in all solvents have been calculated and are presented in Table 4.

The standard Gibbs energy of dissolution is found to be positive in all cases, which means that the solubilization process is apparently not spontaneous. Also, the enthalpy of dissolution is positive in all cases, which suggests that solubilization is always endothermic. Finally, the entropy change is also positive in all cases, indicating that the entropy of dissolution is favorable for all esters in the solvents examined.

Among the three CAEs, MFA demonstrates the highest solubilities in all solvents, which can be explained by its lowest T_m and $\Delta_{fus}H$ values. However, MSA, which has a lower T_m and $\Delta_{fus}H$ than MpCA, has higher solubilities than MpCA only in ethyl acetate and *n*-hexane but not in the two alcohols. This behavior may be explained by the strong intramolecular interactions between the hydroxyl group and the two methoxy groups of the aromatic ring in the MSA molecules, which are required to be broken in order for MSA to be solubilized in associating molecules like *t*-butanol and *t*-pentanol. The high dissolution enthalpies of MSA in the two alcohols (Table 4) confirm this observation.

Taking into consideration the solubility of a particular CAE in the different solvents, it is shown that it is influenced by the polarity of the solvent and the specific interactions encountered (hydrogen bonding). The ranking of the polarity of the solvents examined is the following: ethyl acetate > *t*-pentanol > *t*-butanol > *n*-hexane.[26] *n*-Hexane, which is a nonpolar solvent, is the worst solvent for all three CAEs. For MpCA it is shown that the hydrogen bonding between its hydroxyl and the one of the alcohols leads to a better solvating capacity of the two alcohols than ethyl acetate, with the most polar alcohol (*t*-pentanol) being the best solvent for MpCA. However, for MFA and, especially, MSA, the intramolecular interactions between the hydroxyl group and the methoxy-groups of the aromatic ring weakens the cross-association between the two CAEs and the alcohol molecules and, consequently, the solubilization efficiency of the alcohols. This explains the better solvating capacity of ethyl acetate than *t*-butanol for MFA and than both alcohols for MSA.

In a previous work[18] we have presented the solubilities of the three CAEs in ILs composed of the imidazolium cation and PF_6^- and BF_4^- anions. By comparing the solubilities of the CAEs in the organic solvents measured in this work with those in the ILs, it is concluded that ILs are very competitive to organic solvents, which accounts in favor of the possible replacement of the volatile organic solvents with the nonvolatile ILs.

Finally, the experimentally measured solubilities were correlated with the UNIQUAC and NRTL models. The interaction parameters determined for the two models along with the obtained errors in solubility calculations are presented in Table 5. A very good correlation of the experimental data is obtained by both models, except for the case of MSA/*t*-butanol system, with UNIQUAC being overall only slightly better than NRTL.

Conclusions

The solubilities of three CAEs have been measured in *tert*-butanol, *tert*-pentanol, ethyl acetate, and *n*-hexane, in the temperature range from (303.15 to 321.15) K. It was found that *tert*-pentanol is the best solvent for MpCA and MFA and ethyl acetate for MSA. The melting point temperature and the enthalpy of fusion of the three esters were also measured. The results indicated that the polarity of the solvents and the specific interactions due to hydrogen bonding mainly influence the solubility of the CAEs. Using the experimentally measured solubilities, the thermodynamic properties of dissolution have been calculated. Finally, the UNIQUAC and NRTL models, using two temperature-independent adjustable parameters per binary system, showed a very good description of the solubilities of the CAEs in the organic solvents studied.

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