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# Greener Terpene-Terpene Eutectic Mixtures as Hydrophobic Solvents

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## ABSTRACT

Natural products can be the basis for the development of green solvents, relevant for the advancement of new, more sustainable, processes and products. In this work, ten binary mixtures constituted by terpenes are prepared and characterized. Their solid-liquid phase diagrams show that room temperature solvents can be prepared from solid terpenes in a wide composition range. These diagrams are accurately described by COSMO-RS, showing it to be an useful predictive tool for the design of novel natural solvents. At the eutectic point, these mixtures possess low viscosities, densities lower than water and high boiling temperatures. The low water solubility in the eutectic solvents together with its negligible impact on the properties measured is a strong indicator of the hydrophobic character of these mixtures. The tunable character of these mixtures is demonstrated by studying the solvatochromic parameters in the entire concentration region, being the properties of the final solvents tuned by simply varying

1 the mole fraction of the terpenes. The high potential of this tunable character is shown in the  
2 selective extraction of dyes from their aqueous solutions. This work is expected to devise new  
3 insights concerning these solvents as well as to boost their application in green industrial  
4 processes.  
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10 **Keywords:** Terpenes, Eutectic Mixtures, Tunable, SLE, COSMO-RS, Physicochemical Properties.  
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## Introduction

The growing importance of chemistry founded on sustainable principles has engendered a corresponding necessity in the development of sustainable solvents to further accentuate the green character of developed processes. It is estimated that 20 million MT (metric tons)<sup>1</sup> per annum of organic solvents are industrially produced, the majority from petroleum-based feedstocks. Solvents are ubiquitous in chemistry and are applied as medium for chemical reactions, extraction processes and cleaning processes to name but a few applications. The typically large excess of solvent to solute used results in an excessive and unsustainable consumption of nonrenewable and environmentally questionable chemicals.<sup>2</sup> In this context, the identification of new bio-derived organic solvents capable of replacing the volatile and toxic ones is of the utmost importance.

Terpenes are a well-known class of versatile natural compounds with important applications in various fields.<sup>3</sup> The interesting medical properties of terpenes are extensively reported, showing that they can decrease tumour size, inhibit the growth of cancerous cells, reduce cholesterol levels, and exhibit a biocidal effect on microorganisms in vitro.<sup>4</sup> Additionally, terpenes are used as natural or artificial excipients; namely as solubilisers, permeation enhancers and natural flavorings in pharmaceutical formulations.<sup>5</sup> Pleasant aromas make terpenes and their mixtures essential in many commercial cleaning products, cosmetics and perfumes.<sup>6</sup> In the area of fine chemicals, terpenes like myrcene were investigated as renewable alternatives to petrochemicals,<sup>7</sup> whilst Wu and Davis<sup>8</sup> revealed the bioconversion of algae biomass into terpenes for the production of high energy density aviation fuels. Due to their biodegradable character, terpenes are proposed as bio-derived alternatives to trichloroethane cleaning solvents.<sup>9</sup> Cymene for example is commonly used as a solvent for dyes and varnishes.<sup>10</sup> The similarity of their physico-chemical properties with that of hexane make terpenes an interesting substitute to this petroleum-based solvent.<sup>11</sup>

To date, mixtures of terpenes were mainly investigated in the pharmaceutical field as vehicles for transdermal delivery<sup>12</sup> or as analgesic, antimicrobial and anti-inflammatory vehicles.<sup>13-15</sup> Recently, with the advent of *deep* eutectic solvents (DES),<sup>16</sup> studies involving mixtures of terpenes were extended. Terpene-based hydrophobic eutectic

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3 solvents were proposed as extractants for metals, biomolecules, phytocannabinoids,  
4 lower alcohols, polycyclic aromatic hydrocarbons, and pesticides.<sup>17</sup> In a mixture, the  
5 decrease of the melting point without the formation of a new compound is a feature  
6 that increases the number of potential substances that can be used as solvents. This  
7 allows the use of terpenes with high melting points, since the mixture melting  
8 temperature can be tailored with a second component. Additionally, the mixture  
9 properties can be tuned by selecting the two components and their molar ratio.  
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16 To extend the applications of these solvents to real life scenarios, an accurate  
17 description of their solid-liquid equilibria (SLE) phase diagrams and of their  
18 physicochemical properties is of highest relevance. This allows the user to anticipate  
19 possible incompatibilities between the components, prevent manufacturing problems  
20 and propose innovative solutions in the design of novel, more sustainable processes  
21 based on natural solvents.  
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27 In this work, binary mixtures of L(-)-menthol, thymol, (1R)-(+)-camphor, (-)-borneol or  
28 *trans*-sobrerol are investigated. Their SLE phase diagrams are measured, while the  
29 ability of COSMO-RS to describe them is evaluated. This provides information on the  
30 range of compositions and temperatures for operating these systems as solvents.  
31 Fundamental liquid phase physicochemical properties relevant to their application  
32 including densities and viscosities are reported, and the impact of the water content  
33 upon the properties of the eutectic mixture is addressed. TGA and NMR are employed  
34 to explore the structure of these mixtures, their degradation and purities; and to better  
35 appreciate the interactions of the compounds leading to the eutectic formation. The  
36 Kamlet Taft (KT) solvatochromic parameters are investigated aiming to provide insights  
37 into the nature and characteristics of each solvent and how these characteristics can be  
38 predictively tuned through changes in the mole fraction of the eutectic components.  
39 This versatility in the solvent composition and properties was applied for dye separation,  
40 further highlighting how the separation efficiency can be tuned manipulating the solvent  
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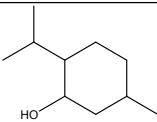
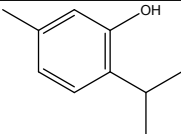
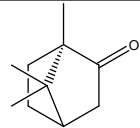
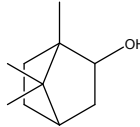
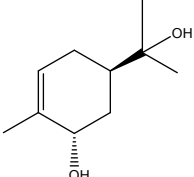
## 54 **Experimental Section**

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## Chemicals

Information on the compounds used in this work is summarized in Table 1 along with the observed rotatory power and melting properties. The terpenes stereochemistry is omitted in the rest of the manuscript. The samples were used as received from the supplier without further purification. Terpenes purity was confirmed by  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra, GC-MS and specific rotation. The ultra-pure water used was double distilled, passed by a reverse osmosis system and further treated with a Milli-Q plus 185 water purification apparatus.

**Table 1.** List of the compounds studied along with their specific rotations ( $[\alpha]_D^{20}$ ) and melting properties ( $T_m$  and  $\Delta_m H$ ).

Compound	$[\alpha]_D^{20}$	Chemical structure	Transition <sup>e</sup>	$T_m / \text{K}$		$\Delta_m H / \text{kJ}\cdot\text{mol}^{-1}$	
				exp.	lit.	exp.	lit.
<b>l(-)-menthol</b> 2216-51-5 Acros Organics wt% = 99.5 <sup>a</sup>	-45.1 <sup>b</sup>		S → L		315.7 ± 0.2 <sup>18</sup>		12.89 ± 0.77 <sup>18</sup>
<b>Thymol</b> 89-83-8 Acros Organics wt% > 99 <sup>a</sup>	0		S → L		323.5 ± 0.3 <sup>18</sup>		19.65 ± 0.42 <sup>18</sup>
<b>(1R)-(+)-camphor</b> 464-49-3 Aldrich wt% = 98 <sup>a</sup>	+41.1 <sup>c</sup>		S <sub>III</sub> → S <sub>II</sub> S <sub>II</sub> → S <sub>I</sub> S <sub>I</sub> → L	241.2 ± 0.1 360.8 ± 2.5 450.4 ± 0.4	242.8 <sup>19</sup> 372.3 <sup>19</sup> 452.7 <sup>19</sup>	12.68 ± 0.03 0.20 ± 0.01 5.28 ± 0.18	11.23 <sup>19</sup> 0.15 <sup>19</sup> 6.3 <sup>20</sup>
<b>(-)-borneol</b> 464-45-9 Sigma-Aldrich wt% ≥ 99 <sup>a</sup>	-34.1 <sup>d</sup>		S <sub>III</sub> → S <sub>II</sub> S <sub>II</sub> → S <sub>I</sub> S <sub>I</sub> → L	214.1 ± 1.0 345.7 ± 1.5 480.6 ± 0.1	213.5 <sup>19</sup> 346.7 <sup>19</sup> 481.6 <sup>19</sup>	1.15 ± 0.01 3.19 ± 0.09 7.60 ± 0.13	0.75 <sup>19</sup> 3.03 <sup>19</sup> 7.3 <sup>21</sup>
<b>trans-sobrerol</b> 42370-41-2 Sigma-Aldrich wt% = 99 <sup>a</sup>	-139.3		S → L	420.2 ± 0.4	423.9 <sup>22</sup>	27.98 ± 0.56	34.81 <sup>22</sup>

<sup>a</sup>Declared by the supplier; <sup>b</sup>Supplier:  $[\alpha]_D^{20} = -51.00$ ; <sup>c</sup>Supplier:  $[\alpha]_D^{25} = +44.1$ ; <sup>d</sup>Supplier:  $[\alpha]_D^{20} = -35.3$ ; <sup>e</sup>S: crystalline solid, L: liquid.

## Mixtures preparation

*Phase Diagrams:* Binary mixtures of terpenes were prepared in different proportions covering the full composition range (at 0.1 mole fraction intervals) using an analytic balance Mettler Toledo XP205. Samples were heated under stirring at a temperature 10 K above the melting temperature of the pure compound with the highest melting point, until a homogenous liquid was formed and then stirred in the liquid state for more 30 minutes. After cooling at room temperature samples of 2 – 5 mg were hermetically sealed in aluminum pans and weighed in a micro-analytical balance AD6 (PerkinElmer, precision = 0.002 mg).

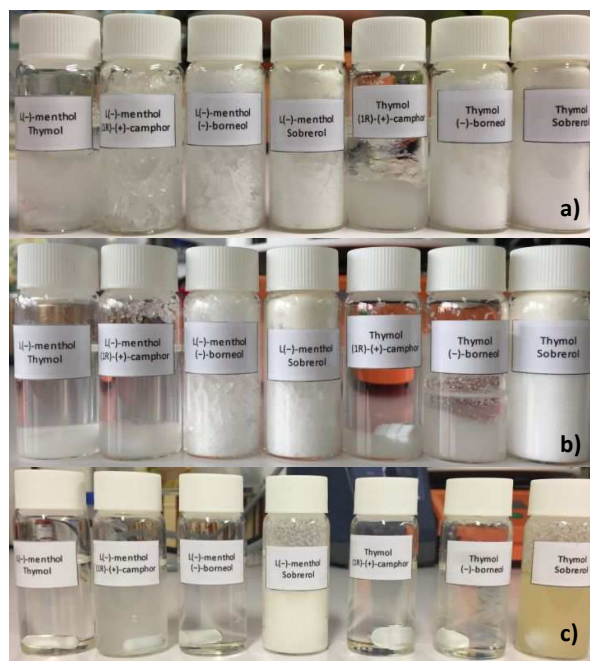
*Eutectic Mixtures:* In order to further characterize the systems under study, one mixture per system with a composition close to the eutectic point (Table 2) was prepared in a larger quantity, following the procedure above. The composition of the eutectic mixtures was confirmed through <sup>1</sup>H-NMR spectroscopy, Figure S1. Since the spectra of the mixtures match the ones from the pure compounds it can also be concluded that no reaction between the mixtures components occurred. After melting and immediate cooling at room temperature, mixtures were stored during 2 days to check their stability – Figure 1. In some cases the mixtures start to become liquid even in the absence of stirring or heating, suggesting the existence of strong interactions between the components. Some systems were not considered in this study due to their high melting points (C+S and B+S) or the nonexistence of a eutectic point (C+B).

**Table 2.** Mole fraction ( $x$ ) of the binary mixtures close to the eutectic point composition.

<i>Abbr.</i>	Mixture Components		$x_1$
	1	2	
M+T	Menthol	Thymol	0.50
M+C	Menthol	Camphor	0.50
M+B	Menthol	Borneol	0.70
M+S	Menthol	Sobrerol	0.95
T+C	Thymol	Camphor	0.50
T+B	Thymol	Borneol	0.50
T+S	Thymol	Sobrerol	0.70
C+B	Camphor	Borneol	- <sup>a</sup>
C+S	Camphor	Sobrerol	0.70

B+S	Borneol	Sobrerol	0.60
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\*The system C+B does not exhibit a eutectic point.



**Figure 1.** Investigated mixtures at room temperature - compositions defined in Table 2: a) immediately after preparation, b) 24 h after preparation without heating or stirring and c) 48 h after preparation by applying 30 min stirring and heating.

*Water-Saturated Eutectic Mixtures:* The impact of water in the physicochemical properties of the eutectic mixtures was here investigated. The above-mentioned eutectic mixtures (at compositions indicated in Table 2) were mixed with ultra-pure water at a 1:1 ratio. Saturation was obtained using an orbital shaker at 323.15 K and 500 rpm during 24 h. The water and organic phases were separated using a centrifuge at 5650 rpm during 30 min with phase separation achieved in all systems. Samples were kept at 323.15 K before any further measurements.

### **Characterization**

*Specific Rotation:* Specific rotations of the pure terpenes were obtained in a solution of ethanol ( $c = 10 \text{ g}/100 \text{ mL}$ ) at 589 nm with an Anton Paar MCP 5100 modular circular polarimeter.



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3 *Differential Scanning Calorimetry (DSC)*: The thermal events of pure terpenes and their  
4 mixtures were obtained using a Hitachi DSC7000X working at atmospheric pressure. The  
5 equipment was previously calibrated with several standards with mass fraction purities  
6 higher than 99%. At least three cycles were performed for the pure compounds and one  
7 for the mixtures. Cooling and heating cycles were performed at 5 K min<sup>-1</sup> and 2 K min<sup>-1</sup>,  
8 respectively. Thermal transitions were taken as the peak temperature. In specific cases  
9 indicated in Tables S1 the melting temperatures were determined: 1) with an automatic  
10 glass capillary device model M-565 from Buchi at 0.1 K min<sup>-1</sup>, being the solid mixtures  
11 firstly grounded and the powder filled into a capillary tube or 2) using a visual method  
12 with an oil bath and a probe (for mixtures with a paste-like appearance). In the latter,  
13 mixtures were gradually heated until complete melting and the temperature was  
14 controlled with a PT100 probe with a precision of ±0.1 K. The probe was previously  
15 calibrated against a calibrated platinum resistance thermometer, SPRT100 (Fluke-Hart  
16 Scientific 1529 Chub-E4), traceable to the National Institute of Standards and  
17 Technology (NIST), with an uncertainty less than 2 × 10<sup>-2</sup> K.  
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30 *X-ray*: The system C+B was analyzed through an x-ray powder diffractometer  
31 (Panalytical Empyrean) operating with Cu anode (K<sub>α1</sub>= 1.5406 Å; K<sub>α2</sub>= 1.5444 Å). The low  
32 temperature chamber was an Anton Paar model TTK450, the temperature controller an  
33 Anton Paar TCU100 and the chamber was cooled using liquid nitrogen. Diffraction data  
34 were collected in the 2θ range from 10° to 40° in steps of 0.026 and a time per step of  
35 50 sec using a linear detector PIXEL 1D with an active length 3.347°, and diffracted  
36 beams anti-scatter slits of 7.5 mm.  
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43 *Thermogravimetric Analysis (TGA)*: Evaporation temperatures of the eutectic mixtures  
44 of terpenes were obtained on a Setsys Evolution 1750 (SETARAM) instrument under air  
45 atmosphere at 10 K min<sup>-1</sup> (precision: temperature ±0.01 K; mass ±0.01 mg).  
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50 *Kamlet Taft Solvatochromic Parameters*: π\*, β and α were measured by adding small  
51 quantities of the probes *N,N*-diethyl-4-nitroaniline, 4-nitroaniline or pyridine-*N*-oxide,  
52 respectively, to the eutectic mixtures,<sup>23,24</sup> which were then stirred (Eppendorf  
53 Thermomixer Comfort) for 30 min at 323.15 K and 2000 rpm. π\* and β were quantified  
54 through the longest wavelength absorption band using UV-Vis spectroscopy (BioTeck  
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Synergy HT microplate reader) at 323.15 K. The  $\alpha$  parameter was determined by  $^{13}\text{C}$  NMR where  $\text{D}_2\text{O}$  in a coaxial insert was used as solvent and trimethylsilyl propanoic acid (TSP) as internal reference. At least three independent measurements were performed for each parameter and mixture.

*Density and viscosity:* Densities and viscosities of the eutectic mixtures and the water saturated eutectic mixtures were measured at atmospheric pressure and at different temperatures using a SVM 3001 Anton Paar viscometer (reproducibility: temperature 0.03 K; density  $0.0001 \text{ g}\cdot\text{cm}^{-3}$ ; viscosity 0.35%).

*Water Content:* The water content of pure terpenes and their eutectic mixtures at room temperature, and the solubility of water in the eutectic mixtures at 323.15 K was evaluated using a Metrohm 831 Karl Fischer coulometer with Hydranal<sup>®</sup>—Coulomat AG, from Riedel-de Haën.

*Nuclear Magnetic Resonance (NMR):* A Bruker Avance 300 operating at 75 MHz was used to analyze the structures of pure terpenes and their eutectic mixtures. Deuterated chloroform ( $\text{CDCl}_3$ ) was used as solvent. The  $^1\text{H}$  NMR spectra obtained confirmed the structures and mole fraction compositions of the prepared eutectic mixtures – Figure S1. Moreover, aiming to investigate the molar ratios in both phases (aqueous and organic) after the addition of water, these were also analyzed. The organic phase was analyzed using  $\text{CDCl}_3$  as a solvent and the water rich phase was analyzed with deuterated water ( $\text{D}_2\text{O}$ ) placed in a coaxial insert. The water peak was suppressed by using the Bruker NMR software.

### **Modeling**

*Solid-Liquid Equilibria:* The phase equilibria of the eutectic mixtures with complete immiscibility in the solid phase can be described by equation (1)

$$\ln(x_i \gamma_i^l) = \frac{\Delta_m H}{R} \left( \frac{1}{T_m} - \frac{1}{T} \right) \quad (1)$$

where  $x_i$  is the mole fraction solubility of compound  $i$  and  $\gamma_i^l$  its activity coefficient in the liquid phase,  $T$  is the absolute temperature,  $T_m$  and  $\Delta_m H$  are the melting

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3 temperature and enthalpy of the pure solute, respectively, and  $R$  is the universal gas  
4 constant.<sup>25</sup> This is a simplified version of the solid-liquid equation where the term  
5 related with heat capacities is neglected due to its small contribution to the phase  
6 equilibrium calculations.<sup>26,27</sup> When ideality is assumed,  $\gamma_i^l = 1$  and the solubility curves  
7 can directly be derived from equation (1). Alternatively, the experimental activity  
8 coefficients can also be obtained through equation (1) using the experimental data.  
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14 *COSMO-RS*: The Conductor-like Screening Model for Real Solvents (*COSMO-RS*) is a  
15 predictive tool for thermophysical properties and phase behavior of pure fluids and  
16 mixtures. It combines quantum chemistry with statistical thermodynamics.<sup>28,29</sup> *COSMO-*  
17 *RS* was used to model the phase diagrams, with all calculations performed using the  
18 software *COSMOtherm*, version 17.0, with the BP\_TZVP\_C30\_1701.ctd parametrization.  
19 The  $\sigma$  profiles needed as input for *COSMO-RS* were prepared with *TURBOMOLE*<sup>30</sup> by  
20 using the *COSMO-BP-TZVP* template of the software package *TmoleX*, version 4.2.1. This  
21 template consists on a def-TZVP basis set and a DFT with the B-P86 functional level of  
22 theory.  
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## 30 **Results and Discussion**

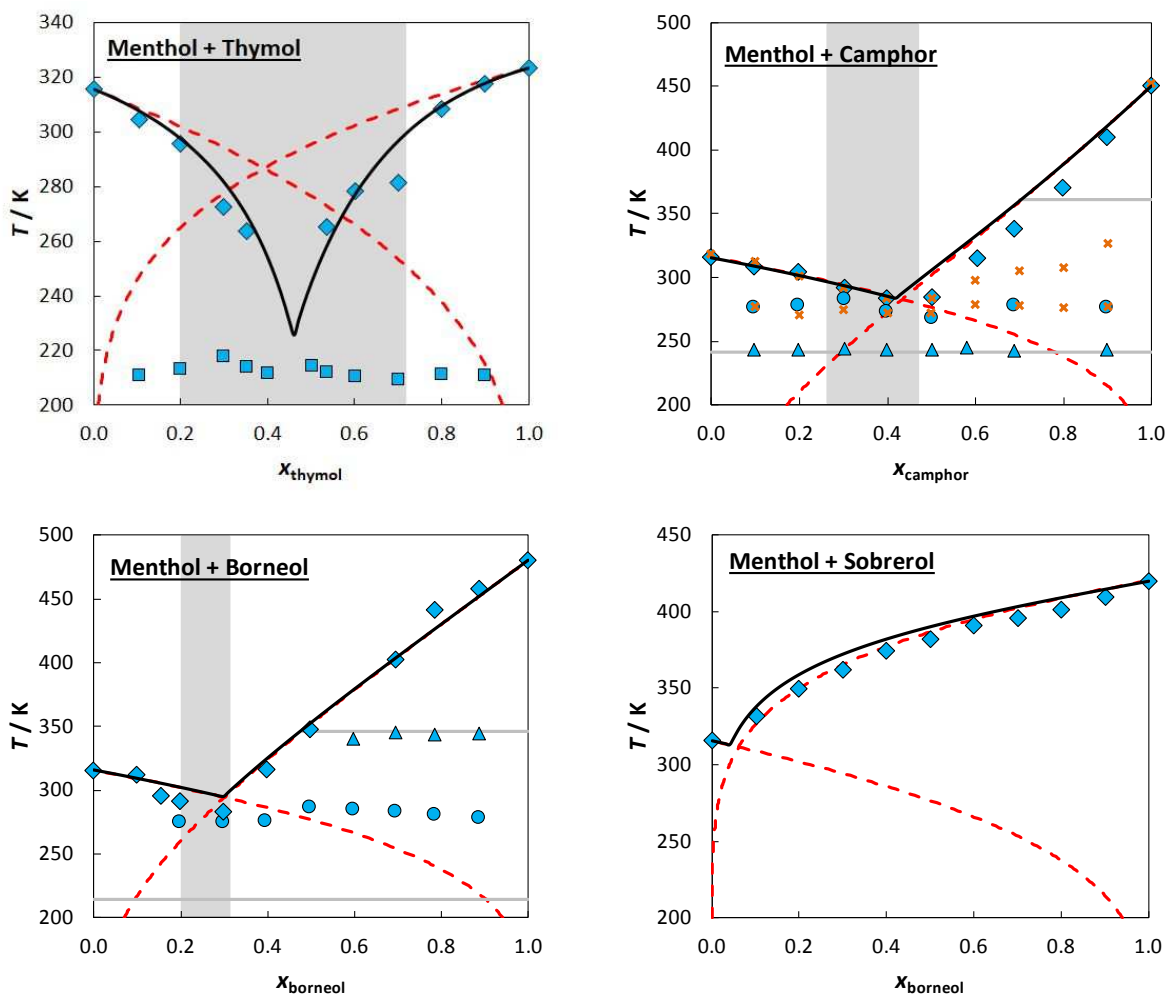
### 31 ***Solid-liquid phase diagrams and COSMO-RS***

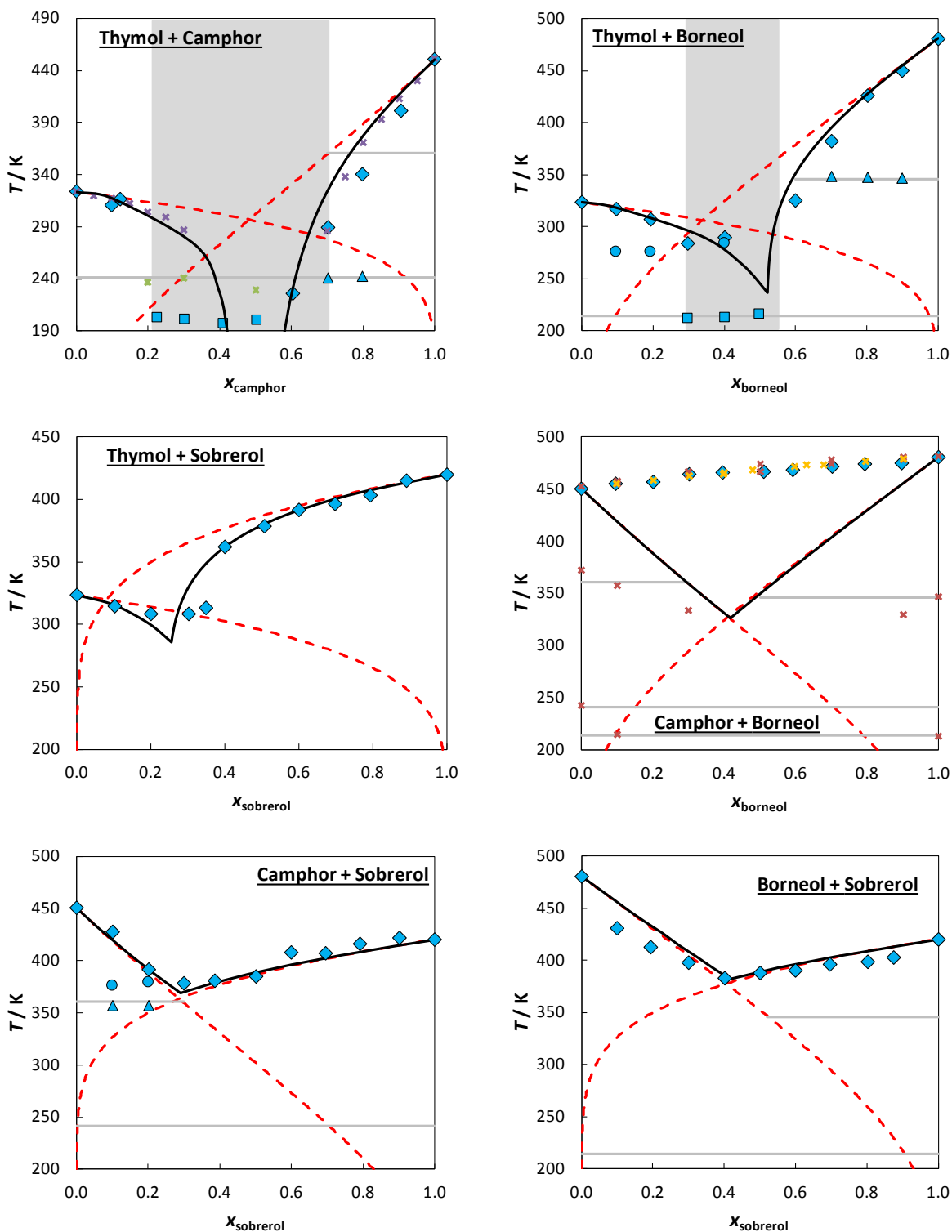
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34 The measured phase diagrams are presented in Figure 2 along with the ideal solubility  
35 curves calculated using equation (1). Detailed experimental data is reported in Tables S1  
36 and S2 of Support Information, along with the activity coefficients estimated from  
37 equation (1). Due to problems in the mixtures crystallization at some compositions or  
38 systems like M+T and T+C, only the glass transitions were observed and are here  
39 reported.  
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48 The melting properties of the pure compounds used in this work are presented in Table  
49 1 along with values from literature. Both sets are in good agreement. Camphor and  
50 borneol present three different solid phases, and their temperatures and enthalpies of  
51 transition were also measured. This subject was also studied before by Chandra and  
52 Murthy.<sup>19</sup> Blokhin et al.<sup>31</sup> investigated in detail the polymorphism of the enantiopure (L-  
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)menthol and found it to have 4 different polymorphs. However in this work, only the stable  $\alpha$  form was detected by DSC.

All mixtures exhibit a phase behavior characterized by a single eutectic point, with the exception of C+B, whose phase diagram indicates the existence of a solid solution in agreement with previously reported observations.<sup>19,32</sup> The formation of a solid solution was further confirmed by X-ray diffraction measurements at 400 K (Figure S2). Results show that the crystal structure remains unchanged (crystal structure: fcc) at different compositions as stated by Chandra and Murthy.<sup>19</sup> The mixture forms a continuous solid solution in phase  $S_1$  which is an orientationally disordered phase.<sup>19</sup>





**Figure 2.** Investigated solid-liquid phase diagrams of mixtures composed of terpenes:  $\blacklozenge$  melting temperatures;  $\blacksquare$ , glass transition temperatures;  $\bullet$ , eutectic temperatures;  $\blacktriangle$ , —, pure terpenes transitions temperatures ( $S_{III} \rightarrow S_{II}$ ,  $S_{II} \rightarrow S_I$ ); - - -, ideal solubility lines;

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3 —, COSMO-RS predictions; ✕, Phaechamud et al.<sup>33</sup>; ✕, Hrynakowski and Szmyt<sup>34</sup>; ✕,  
4 Makoś et al.<sup>35</sup>; ✕, Chandra and Murthy<sup>19</sup>; ✕, Vanstone<sup>32</sup>. Gray regions represent the  
5 concentration range for which the mixture is liquid at room temperature (T = 298.15 K).  
6 M+T phase diagram is adapted from ref.<sup>36</sup>. A closer view of the C+B SLE phase diagram  
7 is provided in Figure S3.  
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12 The SLE phase diagrams of mixtures M+S, M+C, M+B, C+S and B+S present weak  
13 deviations from the ideal behavior, suggesting that hydrogen-bonding networks  
14 established in these systems are not significantly different from those present in the  
15 pure compounds. On the other hand, mixtures involving thymol (M+T,<sup>36</sup> T+C, T+B and  
16 T+S) present strong negative deviations from ideality. The system M+T was studied in  
17 detail by us.<sup>36</sup> The non-ideality was attributed to a strong hydrogen bond established  
18 between the acidic proton of the phenolic hydroxyl of thymol, and the oxygen of the  
19 hydroxyl group of menthol, resulting in much stronger interactions when compared to  
20 the pure compounds.<sup>36</sup> The study of the M+T system allowed the identification of a new  
21 class of eutectic mixtures forming true deep eutectic systems, designated as type V  
22 DES.<sup>36</sup> The strong negative deviations from ideality lead to phase diagrams with regions  
23 where the melting points of the mixtures are close, or below, their glass transition  
24 temperatures. In particular, for mixtures M+T, T+C and T+B, this results in a very large  
25 liquidus region.  
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30 In the literature, SLE phase diagrams of M+C, T+C and C+B were previously  
31 reported.<sup>19,32–35</sup> However, some experimental techniques used are not advisable due to  
32 the non-negligible vapor pressure of these compounds,<sup>21</sup> potentially resulting in  
33 incorrect phase diagrams as shown in Figure 2. The data obtained by Phaechamud et  
34 al.<sup>33</sup> for the system M+C underestimate the melting temperatures in the camphor rich  
35 side. The same is observed for the data reported by Makoś et al.<sup>35</sup> for the system T+C.  
36 The experimental points measured by Hrynakowski and Szmyt<sup>34</sup> for T+C, and by Chandra  
37 and Murthy<sup>19</sup> and Vanstone<sup>32</sup> for C+B are in good agreement with the data measured in  
38 this work.  
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54 COSMO-RS was used to predict the phase diagrams. As can be seen in Figure 2, this tool  
55 is able to successfully describe the SLE of the mixtures, making COSMO-RS a useful tool  
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3 for the *a priori* screening and design of terpenes mixtures. The only exception found is  
4 in the C+B system whose phase diagram indicates the existence of a solid solution. It is  
5 important to highlight the ability of COSMO-RS to correctly describe the non-ideal  
6 behavior of the mixtures containing thymol. The average deviations between COSMO-  
7 RS predicted temperatures and experimental data are reported in Table S3 and are in  
8 the range of 5 to 18 K.  
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14 The melting point depressions for most of the investigated mixtures are considerably  
15 large, but only a few are liquid at room temperature in a wide composition range, even  
16 when both pure compounds are solid. This represents a big advantage since it increases  
17 the flexibility of the relative amounts that can be used, depending on the desired  
18 physical state and properties of the final product.  
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24 In the next sections, the sustainability and applicability of the investigated systems will  
25 be evaluated at the mixture eutectic composition (excepting C+B) studying relevant  
26 properties and features.  
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### 30 ***Thermogravimetric Analysis***

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33 TGA was used to find upper temperature limits at which these systems can be used  
34 (Table 3) without significant mass losses. Thermograms were obtained by measuring the  
35 mass loss under heat conditions in an open system (Figure S4). This is related to  
36 evaporation or sublimation of the compounds, and not to their degradation as  
37 previously stated.<sup>37</sup> Pure components and their mixtures show similar mass loss patterns  
38 with a single-step decay with the exception of C+S and B+S that present a second  
39 plateau. This is attributed to interactions between the pure components that cause  
40 different evaporation temperatures. For these two cases no further analysis are  
41 performed.  
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50 **Table 3.** TGA parameters of the investigated systems.

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<i>System</i>	$x_1$	$T_{\text{onset}} / \text{K}$	$T_{\text{peak}} / \text{K}$
Menthol	-	421.34	458.30
Thymol	-	434.44	473.69

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Camphor	-	438.57	457.07
Borneol	-	428.57	471.72
Sobrerol	-	456.21	501.96
M+T	0.50	451.78	488.24
M+C	0.50	405.08	447.52
M+B	0.70	438.99	472.82
M+S	0.95	418.58	459.21
T+C	0.50	437.44	480.81
T+B	0.50	416.75	461.47
T+S	0.70	451.39	515.40

The mass loss  $T_{\text{onset}}$  ranges from 405 to 456 K corresponding to M+C and pure sobrerol, respectively. In most cases, mixtures presenting an ideal behavior have  $T_{\text{onset}}$  lower or between that of their pure constituents. M+B is an exception, where the  $T_{\text{onset}}$  of the mixture is higher than those of pure menthol and borneol. With the exception of T+B, mixtures involving thymol (i.e., mixtures with a non-ideal behavior) have  $T_{\text{peak}}$  higher than their individual constituents, suggesting the formation of azeotropes. Although there are no VLE data to confirm this hypothesis, such behavior is consistent with the negative deviations observed in the SLE phase diagrams.

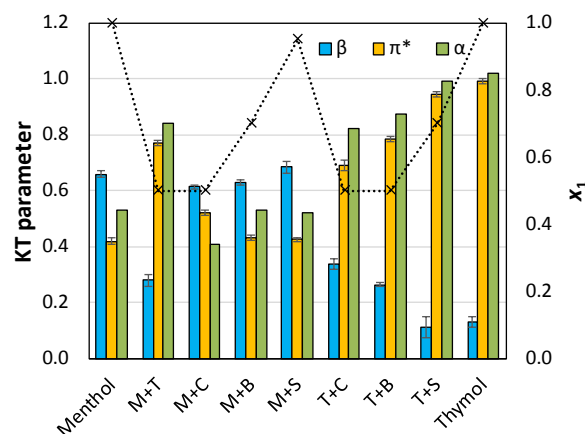
Mixtures involving thymol present a higher operational temperature limit. This is very interesting since these mixtures present large negative deviations from ideality, i.e., a large melting point depression and a wide range of temperature and compositions where the mixtures are in the liquid state. These results are very relevant for industrial applications. Together with the phase diagrams they establish boundary limits in which to apply these mixtures with minimal evaporation losses or crystallization.

### ***Kamlet Taft Solvatochromic Parameters***

Most reactions occur in solution, with the solvent properties influencing its suitability as a reaction or extraction medium. The Kamlet–Taft parameters  $\pi^*$ ,  $\beta$  and  $\alpha$  give information about the polarizability/dipolarity, hydrogen bond acceptor and donor capacity of the mixtures, thereby providing an insight into the nature and characteristics of each solvent. These were here measured at 323.15 K and are presented in Figure 3 and Table S4 (equations available in SI). At this temperature only pure menthol and



thymol are in the liquid state and thus these are the only pure terpenes for which it was possible to measure the KT parameters: menthol<sup>18</sup>  $\beta=0.66$ ;  $\pi^*=0.42$ ;  $\alpha=0.53$  and thymol  $\beta=0.13$ ;  $\pi^*=0.99$ ;  $\alpha=1.02$ . The systems C+S and B+S were not considered here due to the high melting temperatures of their eutectic mixtures.



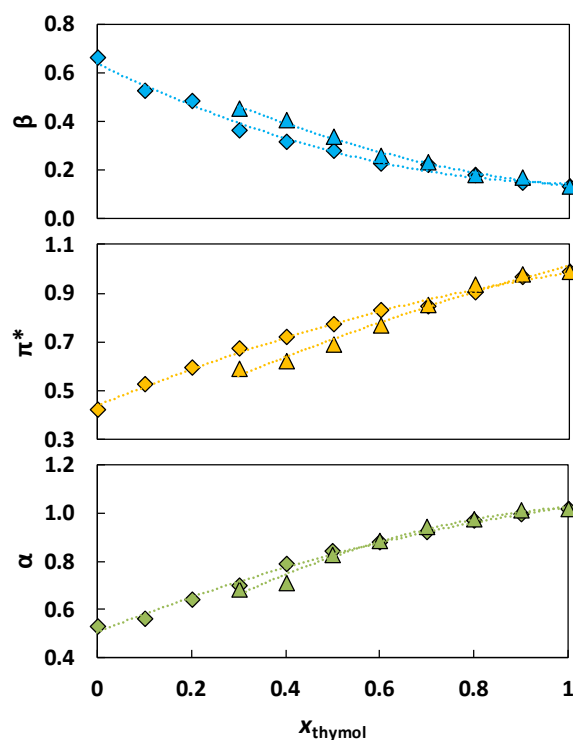
**Figure 3.** Kamlet–Taft solvatochromic parameters of the mixtures at 323.15 K. Clustered columns correspond to the KT parameters (left y-axis) while the dotted line corresponds to the mole fraction of either thymol or menthol (right y-axis).

From Figure 3, mixtures involving thymol present high polarizability/dipolarity as observed before for mixtures of menthol/thymol with monocarboxylic acids.<sup>18</sup> This is related to the presence of the aromatic ring in the thymol structure.<sup>18</sup> Moreover,  $\pi^*$  increases with the increase of thymol content in the mixture. Conversely for mixtures containing menthol,  $\pi^*$  decreases with the increase of menthol content. T+S is the mixture that presents the highest polarizability/dipolarity due to the high content on thymol ( $x_{\text{thymol}} = 0.70$ ).

As observed in our previous work,<sup>18</sup> the variation observed for parameter  $\beta$  is the opposite of parameter  $\alpha$ . Mixtures with menthol present a higher capacity to accept hydrogen bonds that increases with the menthol content in the mixture. The capacity to act as a hydrogen bond donor,  $\alpha$ , is higher in mixtures with thymol. This is in line to what has been discussed above about the acidity of thymol hydroxyl proton.

Mixtures involving camphor display the lowest values of  $\alpha$ , since this ketone does not have the capacity to donate hydrogen bonds according with the sigma profile computed by COSMO-RS (Figure S5). These profiles suggest that sobrerol and thymol have the larger capacity to donate hydrogen bonds (higher  $\alpha$ ) followed by menthol. On the other side, camphor (closely followed by borneol and menthol) seems to be the compound with larger capacity to accept hydrogen bonds and thus should have a higher  $\beta$ . This is in agreement with the experimental KT parameters measured.

When comparing the mixtures evaluated here with common molecular solvents (Table S4) it can be seen that mixtures with thymol present higher  $\pi^*$  values than organic solvents, meaning a higher ability to establish nonspecific interactions with a solute. Additionally, thymol-based mixtures also show hydrogen-bond acidity, which values are in general higher than alcohols, ketones, alkanes and aromatics solvents. The ability to accept protons of the studied mixtures is similar to common alcohols and higher than that of water.



**Figure 4.** Kamlet–Taft solvatochromic parameters of the mixtures  $\blacklozenge$  M+T and  $\blacktriangle$  T+C at 323.15 K as a function of thymol mole fraction. The dotted lines are guides for the eyes.

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3 More importantly, as shown in Figure 3, mixtures of two terpenes can produce different  
4 combinations on the values of  $\pi^*$ ,  $\beta$  and  $\alpha$ , due to the different characteristics of each  
5 solvent that can be tailored for specific applications. Aiming at exploring this topic, the  
6 KT solvatochromic parameters of the mixtures M+T and T+C were measured as a  
7 function of the mole fraction as shown in Figure 4. In both systems, the parameters  $\pi^*$   
8 and  $\alpha$  increase with the increase molar fraction of thymol while  $\beta$  shows the opposite  
9 behavior covering wide ranges of these parameters. This shows how the desired  
10 properties of the final solvent can be tailored based on the mole fraction of the  
11 constituents rather than using always the eutectic point composition or a well-defined  
12 molar ratio.  
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### 21 ***Densities and Viscosities***

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24 To minimize mass transfer limitations, an ideal solvent should have a low viscosity, and  
25 for extraction purposes its density should be sufficiently different from the water density  
26 to ease phase separation. Here, these physicochemical properties were investigated  
27 aiming to evaluate the applicability of the mixtures under study.  
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32 Densities and viscosities of the terpene-based mixtures at the eutectic composition,  
33 both dry and water-saturated, were measured at atmospheric pressure in the  
34 temperature range from 278.15 to 373.15 K. The results are displayed in Figures S6 and  
35 S7 and listed in Tables S5-S8. The water content of pure terpenes and their mixtures is  
36 presented in Table S9. Systems T+S, C+S and B+S were not considered here due to the  
37 high melting temperatures of their eutectic points. Densities and viscosities of pure  
38 thymol and menthol were previously reported by us.<sup>38</sup>  
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45 All systems measured present densities lower than water. Viscosities decrease with the  
46 addition of water, while densities increase in the same conditions. As observed for  
47 mixtures with monocarboxylic acids,<sup>18</sup> mixtures containing thymol present higher  
48 densities than those with menthol. The density of pure menthol is lower than the  
49 densities of any of the mixtures considered at all temperatures, while the density of pure  
50 thymol is in between the density of T+C and T+B. Regarding viscosities, pure thymol  
51 presents lower viscosities than all the mixtures studied. At moderate and high  
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3 temperatures viscosities are very low and similar. At 298.15 K, viscosities vary from 16  
4 to 110 mPa corresponding to M+C and M+B, respectively. By adding water, these values  
5 decrease to 15 and 74 mPa with water content of around 2200 and 17000 ppm (without  
6 and with water saturation, respectively). Due to its lower value and despite the increase  
7 in the water content after the saturation of the mixture, the viscosity of the system M+C  
8 remains approximately constant.  
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14 Osch et al.<sup>37</sup> reported values for the water content, density and viscosity of the system  
15 M+T (1:1): 306.8 ppm (295.15 K), 0.9366 g·cm<sup>-3</sup> (298 K) and 53.14 mPa·s (298 K),  
16 respectively. Significant differences were obtained here for the water content (3059  
17 ppm) and consequently, for viscosity (38.08 mPa·s). This may be attributed to the  
18 stereoisomer of menthol used. Here l(-)-menthol (CAS: 2216-51-5) was used while  
19 authors used a racemic mixture dl-menthol (CAS: 89-78-1).  
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26 When in equilibrium with water, some of the eutectic mixture will partition to the water  
27 phase and, as reported in Table S9, a certain quantity of water will solubilize in the  
28 eutectic mixture. The water content of the pure compounds and their mixtures with and  
29 without saturation with water varies between 79 and 23545 ppm (Table S9), increasing  
30 after the saturation with water due to the solubility of water in the mixture. However,  
31 the solubility of water in the eutectic mixtures is in general low (12209 – 23545 ppm),  
32 demonstrating the hydrophobic character of these binary mixtures  
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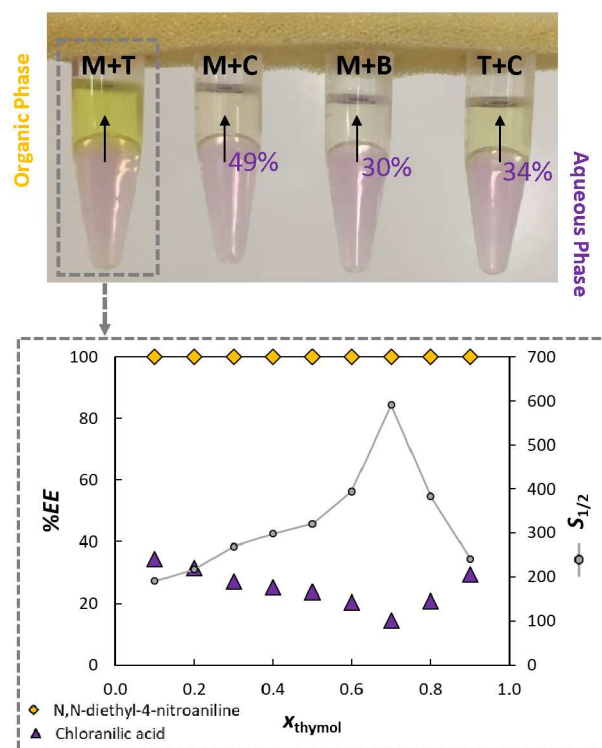
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39 <sup>1</sup>H-NMR analysis of the eutectic systems and water phases after mutual saturation was  
40 performed and the results are reported in Figure S8. The mole ratio of the pure  
41 compounds in the organic phase is, after mixing with water, the same as the original.  
42 After saturation, the water peak (≈1.56 ppm) is visible in the systems M+C and M+B. The  
43 water phase was evaluated by suppressing the water peak. The ratio of the terpenes in  
44 the aqueous phase was evaluated for the systems M+T, M+C and T+C. The changes  
45 observed from the original composition are in line with the solubilities of the pure  
46 terpenes in water. For instance, the composition prepared for the M+T system was  
47 0.5:0.5 and after equilibrium, the ratio of terpenes in the aqueous phase was estimated  
48 to be 0.13:0.87 due to the higher solubility of thymol in water, 9.84×10<sup>-4</sup> g/g<sub>H2O</sub>, when  
49 compared to the solubility of menthol, 6.27×10<sup>-4</sup> g/g<sub>H2O</sub>.<sup>39,40</sup> The system M+C is  
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3 apparently an exception since the terpenes ratio in the water phase does not  
4 correspond to the relative solubility of the pure terpenes in water. This can be attributed  
5 to the NMR accuracy. For the other systems no isolated peaks could be assigned to the  
6 components of the mixtures, preventing the analysis in the aqueous phase.  
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10 Summarizing, the viscosities of the mixtures investigated are slightly greater than that  
11 of conventional organic solvent but significantly less than those for ionic DES.  
12 Furthermore, the reported densities are sufficiently different from the water density,  
13 indicating that these systems can be interesting options for industrial applications.  
14 Additionally, the water solubility on these mixtures is quite low, thus showing a low  
15 ability to absorb water from the atmosphere, or during extraction processes.  
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### 22 **Tailored Extraction**

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24 The properties of the proposed eutectic solvents can be selectively tuned changing the  
25 components as well as their respective composition. In this section, this flexibility in the  
26 eutectic properties was applied to the selective separation of two dyes, *N,N*-diethyl-4-  
27 nitroaniline and chloranilic acid, from its mixture in water. Eutectic mixtures were  
28 contacted with the dyes aqueous solution. The organic to aqueous phase ratio was of 1  
29 and the volume of each phase remained constant after extraction. The detailed  
30 experimental equations are available in SI. The extraction of the respective dyes and  
31 their mutual separation is shown in Figure 5. An example of the UV-Vis spectra of the  
32 aqueous and eutectic phases before and after extraction is presented in Figure S9.  
33 Results indicate a good separation with *N,N*-diethyl-4-nitroaniline (yellow) (1) that is  
34 quantitatively extracted to the organic phase for all compositions (distribution ratio  
35  $D_{N,N\text{-diethyl-4-nitroaniline}} = 100$  – assuming quantitative extraction). In contrast, the extraction  
36 of chloranilic acid (purple) (2) is strongly influenced by the terpene selection as well as  
37 by the molar composition of the eutectic formulation. The extraction of chloranilic acid  
38 to the eutectic phases varies from 14% to 49% from M+T (0.3:0.7) to M+C (0.5:0.5)  
39 respectively. Additionally, as observed for the system M+T, the selectivity (*S*) almost  
40 tripled by changing the mole fraction of the compounds in the terpene mixture. An  
41 effective separation was obtained with a maximum separation factor of around 600  
42 when using 70% of thymol in the eutectic mixture.  
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**Figure 5.** Separation of dyes *N,N*-diethyl-4-nitroaniline (1-yellow) and chloranilic acid (2-purple) in mixtures of terpenes and water.

Aiming at design green solvents to be used in industry, a wide variety of terpene-based eutectic mixtures were prepared and characterized. The SLE phase diagrams were measured in the whole composition range showing significant melting point depression. Liquid solvents can be obtained for some of these mixtures in a wide composition and temperature range. The COSMO-RS was shown to be able to predict the phase behaviour of these mixtures, including the systems of thymol with remarkable strong negative deviations from ideality. This model can thus be used to design new eutectic mixtures. The eutectic mixtures present high boiling temperatures, densities lower than water and low viscosities – important parameters when envisioning industrial applications. The solubility of water in the eutectic systems is quite low and it has a low impact in the properties measured, demonstrating the hydrophobic character of these mixtures and preventing their loss and contamination to the aqueous phase.

The solvatochromic parameters show that the mixtures with menthol present a higher capacity to accept hydrogen bonds while the capacity to act as a hydrogen bond donor

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3 is higher in mixtures with thymol. More importantly, the characteristics of the final  
4 solvent can be tailored since different mixtures give different combinations of  $\pi^*$ ,  $\beta$  and  
5  $\alpha$ .  
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9 This flexibility in the solvent characteristics was applied to the selective and tunable  
10 separation of dyes from water, where changes in the eutectic components and their  
11 mole fraction, affect the separation factor. No volume change is observed for the  
12 different systems reinforcing the idea that a total separation of the organic and water  
13 phases occurs, and attesting to the hydrophobic character of the systems investigated.  
14 It was also proved that the extraction and selectivity can be manipulated by varying the  
15 mole fraction of the terpenes in the mixture.  
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## 22 **Supporting Information**

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25 NMR spectra of pure terpenes and their mixtures; experimental SLE phase diagrams  
26 data and activity coefficients; X-ray diffractogram of C+B; AAD between COSMO-Rs  
27 predictions and experimental data; TGA thermograms; KT solvatochromic parameters  
28 and equations; sigma profiles of pure terpenes; densities and viscosities; water  
29 contents; NMR spectra of aqueous and organic phases after equilibrium.  
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## 55 **References**

- 1  
2  
3 (1) Clark, J.; Farmer, T.; Hunt, A.; Sherwood, J.; Clark, J. H.; Farmer, T. J.; Hunt, A. J.; Sherwood, J.  
4 Opportunities for Bio-Based Solvents Created as Petrochemical and Fuel Products Transition  
5 towards Renewable Resources. *Int. J. Mol. Sci.* **2015**, *16* (8), 17101–17159, DOI  
6 10.3390/ijms160817101.
- 7  
8 (2) Clarke, C. J.; Tu, W.-C.; Levers, O.; Bröhl, A.; Hallett, J. P. Green and Sustainable Solvents in  
9 Chemical Processes. *Chem. Rev.* **2018**, *118* (2), 747–800, DOI 10.1021/acs.chemrev.7b00571.
- 10  
11 (3) Zwenger, S.; Basu, C. Plant Terpenoids: Applications and Future Potentials. *Biotechnol. Mol. Biol.*  
12 *Rev.* **2008**, *3* (1), 1–7, DOI 10.5897/BMBR.
- 13  
14 (4) Adrian Davis. Topical Pharmaceutical Compositions, 2014.
- 15  
16 (5) Balbani, A. P. S.; Stelzer, L. B.; Montovani, J. C. Pharmaceutical Excipients and the Information on  
17 Drug Labels. *Braz. J. Otorhinolaryngol.* **2006**, *72* (3), 400–406, DOI 10.1016/S1808-8694(15)30976-  
18 9.
- 19  
20 (6) Tetali, S. D. Terpenes and Isoprenoids: A Wealth of Compounds for Global Use. *Planta* **2019**, *249*  
21 (1), 1–8, DOI 10.1007/s00425-018-3056-x.
- 22  
23 (7) Behr, A.; Johnen, L. Myrcene as a Natural Base Chemical in Sustainable Chemistry: A Critical  
24 Review. *ChemSusChem* **2009**, *2* (12), 1072–1095, DOI 10.1002/cssc.200900186.
- 25  
26 (8) Wu, W.; Davis, R. W. One-Pot Bioconversion of Algae Biomass into Terpenes for Advanced Biofuels  
27 and Bioproducts. *Algal Res.* **2016**, *17*, 316–320, DOI 10.1016/J.ALGAL.2016.05.005.
- 28  
29 (9) Brown, L. M.; Springer, J.; Bower, M. Chemical Substitution for 1,1,1-Trichloroethane and  
30 Methanol in an Industrial Cleaning Operation. *J. Hazard. Mater.* **1992**, *29* (2), 179–188, DOI  
31 10.1016/0304-3894(92)85068-C.
- 32  
33 (10) Corma, A.; Iborra, S.; Velty, A. Chemical Routes for the Transformation of Biomass into Chemicals.  
34 *Chem. Rev.* **2007**, *107* (6), 2411–2502, DOI 10.1021/cr050989d.
- 35  
36 (11) Yara-Varón, E.; Selka, A.; Fabiano-Tixier, A. S.; Balcells, M.; Canela-Garayoa, R.; Bily, A.; Touaibia,  
37 M.; Chemat, F. Solvent from Forestry Biomass. Pinane a Stable Terpene Derived from Pine Tree  
38 Byproducts to Substitute n-Hexane for the Extraction of Bioactive Compounds. *Green Chem.* **2016**,  
39 *18* (24), 6596–6608, DOI 10.1039/C6GC02191C.
- 40  
41 (12) Gala, U.; Pham, H.; Chauhan, H. Pharmaceutical Applications of Eutectic Mixtures. *J. Dev. Drugs*  
42 **2013**, *2* (3), 1–2, DOI 10.4172/2329-6631.1000e130.
- 43  
44 (13) Stott, P. W.; Williams, A. C.; Barry, B. W. Transdermal Delivery from Eutectic Systems: Enhanced  
45 Permeation of a Model Drug, Ibuprofen. *J. Control. Release* **1998**, *50* (1), 297–308, DOI  
46 10.1016/S0168-3659(97)00153-3.
- 47  
48 (14) Yong, C. S.; Oh, Y.-K.; Jung, S. H.; Rhee, J.-D.; Kim, H.-D.; Kim, C.-K.; Choi, H.-G. Preparation of  
49 Ibuprofen-Loaded Liquid Suppository Using Eutectic Mixture System with Menthol. *Eur. J. Pharm.*  
50 *Sci.* **2004**, *23* (4–5), 347–353, DOI 10.1016/j.ejps.2004.08.008.
- 51  
52  
53  
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56  
57  
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59  
60



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2  
3 (15) Kang, L.; Jun, H. W.; McCall, J. W. Physicochemical Studies of Lidocaine-Menthol Binary Systems  
4 for Enhanced Membrane Transport. *Int. J. Pharm.* **2000**, *206* (1–2), 35–42, DOI 10.1016/S0378-  
5 5173(00)00505-6.
- 6  
7 (16) Abbott, A. P.; Capper, G.; Davies, D. L.; Rasheed, R. K.; Tambyrajah, V. Novel Solvent Properties of  
8 Choline Chloride/Urea Mixtures. *Chem. Commun.* **2003**, *99* (1), 70–71, DOI 10.1039/b210714g.
- 9  
10 (17) Dwamena, A. K.; Dwamena, K., A. Recent Advances in Hydrophobic Deep Eutectic Solvents for  
11 Extraction. *Separations* **2019**, *6* (1), 9, DOI 10.3390/separations6010009.
- 12  
13 (18) Martins, M. A. R.; Crespo, E. A.; Pontes, P. V. A.; Silva, L. P.; Bülow, M.; Maximo, G. J.; Batista, E.  
14 A. C.; Held, C.; Pinho, S. P.; Coutinho, J. A. P. Tunable Hydrophobic Eutectic Solvents Based on  
15 Terpenes and Monocarboxylic Acids. *ACS Sustain. Chem. Eng.* **2018**, *6* (7), 8836–8846, DOI  
16 10.1021/acssuschemeng.8b01203.
- 17  
18 (19) Chandra, G.; Murthy, S. S. N. Dielectric and Thermodynamic Study of Camphor and Borneol  
19 Enantiomers and Their Binary Systems. *Thermochim. Acta* **2018**, *666*, 241–252, DOI  
20 10.1016/j.tca.2018.04.014.
- 21  
22 (20) Rietveld, I. B.; Barrio, M.; Veglio, N.; Espeau, P.; Tamarit, J. L.; Céolin, R. Temperature and  
23 Composition-Dependent Properties of the Two-Component System d- and l-Camphor at  
24 ‘Ordinary’ Pressure. *Thermochim. Acta* **2010**, *511* (1–2), 43–50, DOI  
25 <http://dx.doi.org/10.1016/j.tca.2010.07.023>.
- 26  
27 (21) Štefja, V.; Fulem, M.; Růžička, K.; Červinka, C. Thermodynamic Study of Selected Monoterpenes II.  
28 *J. Chem. Thermodyn.* **2014**, *79*, 272–279, DOI 10.1016/j.jct.2013.12.012.
- 29  
30 (22) Bettinetti, G.; Giordano, F.; Fronza, G.; Italia, A.; Pellegata, R.; Villa, M.; Ventura, P. Sobrerol  
31 Enantiomers and Racemates: Solid-State Spectroscopy, Thermal Behavior, and Phase Diagrams. *J.*  
32 *Pharm. Sci.* **1990**, *79* (6), 470–475, DOI 10.1002/jps.2600790603.
- 33  
34 (23) Schneider, H.; Badrieh, Y.; Migron, Y.; Marcus, Y. Hydrogen Bond Donation Properties of Organic  
35 Solvents and Their Aqueous Mixtures from 13 C NMR Data of Pyridine-n-Oxide. *Zeitschrift für Phys.*  
36 *Chemie* **1992**, *177* (2), 143–156, DOI 10.1524/zpch.1992.177.Part\_2.143.
- 37  
38 (24) Teles, A. R. R.; Capela, E. V.; Carmo, R. S.; Coutinho, J. A. P.; Silvestre, A. J. D.; Freire, M. G.  
39 Solvatochromic Parameters of Deep Eutectic Solvents Formed by Ammonium-Based Salts and  
40 Carboxylic Acids. *Fluid Phase Equilib.* **2017**, *448*, 15–21, DOI 10.1016/j.fluid.2017.04.020.
- 41  
42 (25) Prausnitz, J. M.; Lichtenthaler, R. N.; Azevedo, E. G. *Molecular Thermodynamics Fluid Phase*  
43 *Equilibria*; Prentice-Hall, 1986.
- 44  
45 (26) Gmehling, J.; Kolbe, B.; Kleiber, M.; Rarey, J. *Chemical Thermodynamics for Process Simulation*;  
46 Wiley-VCH, 2012.
- 47  
48 (27) Coutinho, J. A. P.; Andersen, S. I.; Stenby, E. H. Evaluation of Activity Coefficient Models in  
49 Prediction of Alkane Solid-Liquid Equilibria. *Fluid Phase Equilib.* **1995**, *103* (1), 23–39, DOI  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

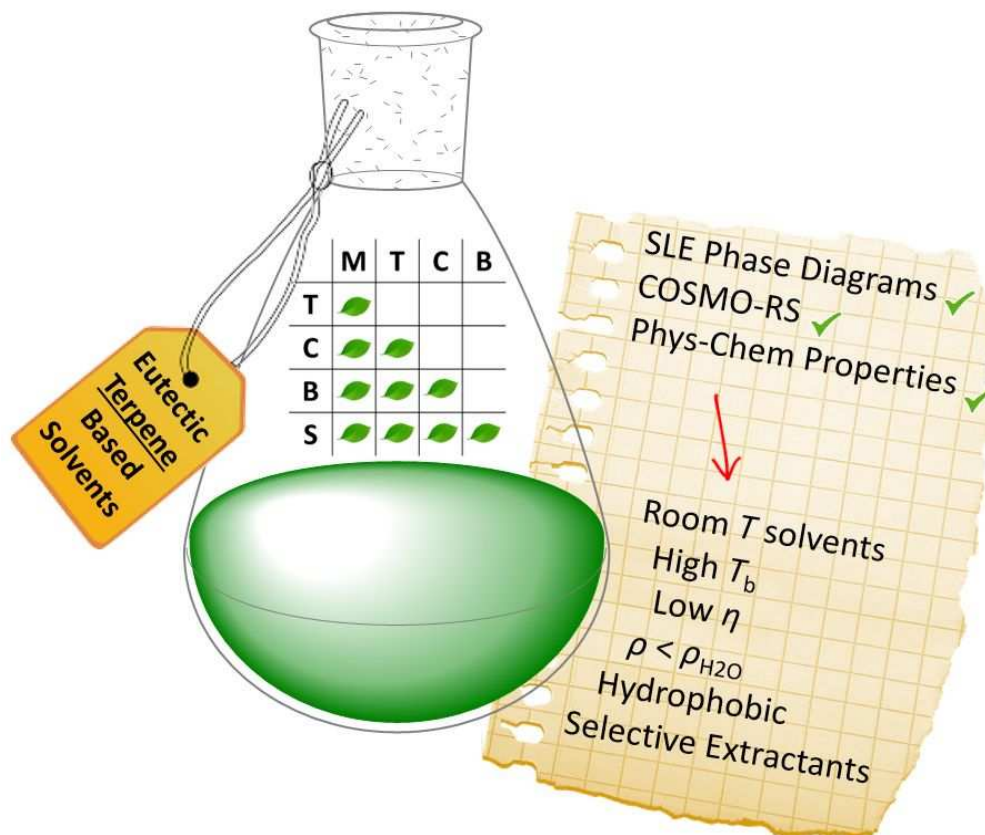
- 1  
2  
3 10.1016/0378-3812(94)02600-6.  
4  
5 (28) Klamt, A. Conductor-like Screening Model for Real Solvents: A New Approach to the Quantitative  
6 Calculation of Solvation Phenomena. *J. Phys. Chem.* **1995**, *99* (7), 2224–2235, DOI  
7 10.1021/j100007a062.  
8  
9 (29) Klamt, A. *COSMO-RS From Quantum Chemistry to Fluid Phase Thermodynamics and Drug Design*;  
10 Elsevier: Amsterdam, The Netherlands, 2005.  
11  
12 (30) TURBOMOLE, a Development of University of Karlsruhe and Forschungszentrum Karlsruhe GmbH,  
13 1989–2013, TURBOMOLE GmbH, since 2007; [Http://www.Turbomole.Com/](http://www.turbomole.com/).  
14  
15 (31) Štejfa, V.; Bazyleva, A.; Fulem, M.; Rohlíček, J.; Skořepová, E.; Růžička, K.; Blokhin, A. V.  
16 Polymorphism and Thermophysical Properties of L- and DL-Menthol. *J. Chem. Thermodyn.* **2019**,  
17 *131*, 524–543, DOI 10.1016/j.jct.2018.11.004.  
18  
19 (32) Vanstone, E. LXXVI.—The Miscibility of Solids. *J. Chem. Soc., Trans.* **1909**, *95* (0), 590–604, DOI  
20 10.1039/CT9099500590.  
21  
22 (33) Phaechamud, T.; Tuntarawongsa, S.; Charoensuksai, P. Evaporation Behavior and Characterization  
23 of Eutectic Solvent and Ibuprofen Eutectic Solution. *AAPS PharmSciTech* **2016**, *17* (5), 1213–1220,  
24 DOI 10.1208/s12249-015-0459-x.  
25  
26 (34) Hrynakowski, K.; Szmyt, M. Die Heterogenen Gleichgewichte in Zweistoffsystemen Mit Thymol Als  
27 Einer Komponente. *Arch. Pharm. (Weinheim)*. **1935**, *273* (25–28), 418–427, DOI  
28 10.1002/ardp.19352732509.  
29  
30 (35) Makoś, P.; Przyjazny, A.; Boczkaj, G. Hydrophobic Deep Eutectic Solvents as “Green” Extraction  
31 Media for Polycyclic Aromatic Hydrocarbons in Aqueous Samples. *J. Chromatogr. A* **2018**, *1570*,  
32 28–37, DOI 10.1016/J.CHROMA.2018.07.070.  
33  
34 (36) Abranches, D. O.; Martins, M.; Silva, L.; Schaeffer, N.; Pinho, S. P.; Coutinho, J. A. P. Phenolic  
35 Hydrogen Bond Donors in the Formation of Non-Ionic Deep Eutectic Solvents: The Quest for Type  
36 V DES. *Chem. Commun.* **2019**, *55*, 10253–10256, DOI 10.1039/c9cc04846d.  
37  
38 (37) Van Osch, D. J. G. P.; Dietz, C. H. J. T.; Van Spronsen, J.; Kroon, M. C.; Gallucci, F.; Van Sint Annaland,  
39 M.; Tuinier, R. A Search for Natural Hydrophobic Deep Eutectic Solvents Based on Natural  
40 Components. *ACS Sustain. Chem. Eng.* **2019**, *7* (3), 2933–2942, DOI  
41 10.1021/acssuschemeng.8b03520.  
42  
43 (38) Martins, M. A. R.; Carvalho, P. J.; Palma, A. M.; Domańska, U.; Coutinho, J. A. P.; Pinho, S. P.  
44 Selecting Critical Properties of Terpenes and Terpenoids through Group-Contribution Methods  
45 and Equations of State. *Ind. Eng. Chem. Res.* **2017**, *56* (35), 9895–9905, DOI  
46 10.1021/acs.iecr.7b02247.  
47  
48 (39) Martins, M. A. R.; Silva, L. P.; Ferreira, O.; Schröder, B.; Coutinho, J. A. P.; Pinho, S. P. Terpenes  
49 Solubility in Water and Their Environmental Distribution. *J. Mol. Liq.* **2017**, *241*, 996–1002, DOI  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 10.1016/j.molliq.2017.06.099.

- 4 (40) Ajisaka, N.; Hara, K.; Mikuni, K.; Hashimoto, H. Effects of Branched Cyclodextrins on the Solubility  
5 and Stability of Terpenes. *Biosci. Biotechnol. Biochem.* **2000**, *64* (4), 731–734, DOI  
6 10.1271/bbb.64.731.  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
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## Synopsis

Design and characterization of greener and tunable hydrophobic eutectic solvents composed of terpenes.