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Using COSMO-RS to design organic biphasic systems containing deep eutectic solvents for the separation of natural compounds

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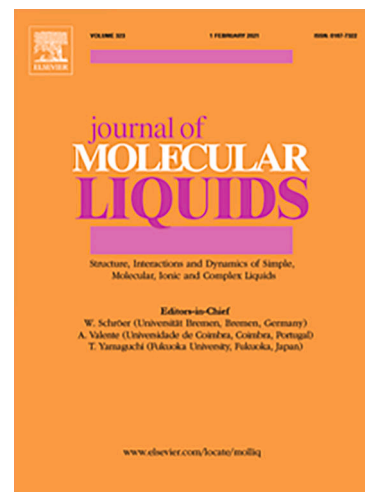
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1 **Using COSMO-RS to design organic biphasic systems containing deep eutectic**
2 **solvents for the separation of natural compounds.**

3

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9 **Highlights**

10 **COSMO-RS was used to predict properties of organic biphasic systems containing deep eutectic**
11 **solvents.**

12 **Biphasic systems studied theoretically aim to be applied to the separation of natural compounds.**

13 COSMO-RS predicted well binodal curves and phase compositions of 4 components DES-based
14 biphasic systems.

15 Good prediction of partition coefficients were obtained for natural compounds in DES-based
16 systems.

17

18 **Abstract**

19 This study is aimed at evaluating the potential of the conductor-like screening model for real solvents
20 (COSMO-RS) in designing biphasic systems for the separation of natural compounds. This model was
21 used to predict binodal curves and phases composition of organic biphasic systems containing deep
22 eutectic solvents. The results obtained demonstrate that COSMO-RS in most cases predict the binodal
23 curves of the biphasic systems with a good precision. Moreover, the partition coefficients of six natural
24 compounds, namely quercetin, apigenin, coumarin, β -ionone, retinol, and α -tocopherol, were
25 evaluated, with COSMO-RS predictions showing excellent agreement with experimental data when the
26 compound partition significantly in both phases. Furthermore, COSMO-RS was able to effectively
27 capture the influence of changes in the system composition on partition coefficients. Thus, these
28 results indicate that COSMO-RS can be a powerful tool in the design of separation and purification
29 systems.

30

31 **Keywords**

32 *Thermodynamic modelling, COSMO-RS, deep eutectic solvents, phase diagrams, natural compounds,*
33 *partitioning*

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38 1. Introduction

39

40 Over the last decade, chemical processes that use solvents produced from renewable resources have
41 gained significant attention in the context of sustainable development. [1] Deep eutectic solvents (DES)
42 are a relatively new class of green solvents that were first proposed by Abbott et al.[2] They are a
43 mixture of hydrogen bond acceptor (HBA) and hydrogen bond donor (HBD) compounds, which exhibit
44 a significant negative deviation in melting point to ideal liquid mixtures.[3] The large deviation in
45 melting point is due to specific interactions, such as hydrogen bonding interactions, between
46 components of the mixture.[4] Recently, less toxic and more environmentally friendly HBA and HBD
47 compounds from renewable sources have been used to prepare deep eutectic solvents.

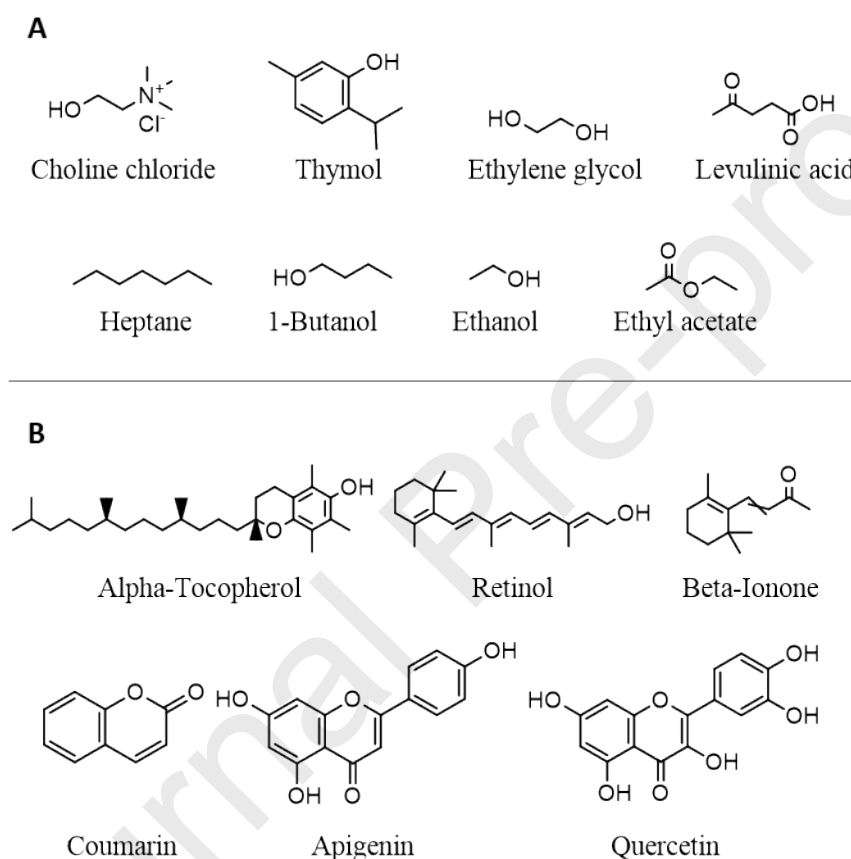
48 Several studies have shown that DES can induce a phase separation when mixed with two miscible
49 organic solvents. The biphasic systems formed are useful for partitioning natural compounds using
50 techniques such as centrifugal partition chromatography (CPC).[5–7] However, because of the large
51 number of DES available and the even larger number of organic biphasic systems (OBS) where they can
52 be used, and because of the diversity of extractable natural compounds, experimental screening of
53 such solvent systems and natural compounds as well as optimization of such separation systems is
54 time-consuming and tedious. In the specific case of CPC, good separation of analytes is generally
55 achieved with solvent system yielding partition coefficients for analytes ranging from 0.5 to 3 and
56 differing as much as possible from one another.[8]

57 To overcome this experimental issue, a theoretical approach, the conductor-like screening model for
58 real solvents (COSMO-RS), has gathered a lot of attention. This model is based on the description of
59 molecules using quantum chemical calculations and predicts thermodynamic properties of chemical
60 solutions, including vapor-liquid, liquid-liquid, and solid-liquid equilibria of chemical mixtures. [9–11]
61 Such a model is useful for calculating phase diagrams of solvent mixtures as well as partition
62 coefficients of natural compounds in biphasic mixtures. COSMO-RS has been previously applied to
63 alternative solvents to predict liquid-liquid equilibrium of binary systems based on ionic liquid and
64 water[12] or alcohols, [13] and various other molecular solutes.[14] Additionally, it has been
65 extensively used in order to study ternary liquid-liquid equilibrium, including systems containing ionic
66 liquids mixed with either aromatic and aliphatic compounds [15], or organic solvents and water.[16]
67 Liquid-liquid equilibrium of several systems containing a DES and organic solvents were also reported.
68 [7,17,18] Recently, we have used COSMO-RS in order to predict binodal curves for biphasic systems
69 containing heptane, ethanol, and either HBD compounds, such as glycerol, ethylene glycol, levulinic
70 acid, or the corresponding choline chloride-based DES. Moreover, it has been used to predict partition
71 coefficients of natural compounds in these biphasic systems. [7]

72 Recently, experimental binodal curves for organic biphasic systems containing heptane, a DES based
73 on choline chloride or thymol, and either ethanol, 1-butanol or ethyl acetate were measured by our
74 group using cloud point titration, along with the partition coefficients of natural compounds in the
75 corresponding reported systems.[19] As part of an ongoing effort to use COSMO-RS model as a
76 predictive tool for optimizing new biphasic systems for the purification of natural compounds, in this
77 manuscript we first evaluate the performance of COSMO-RS in the prediction of binodal curves of
78 these systems. Various approaches to describe choline chloride with COSMO-RS will be explored and

79 their impact on the calculations of the phase compositions formed with selected biphasic mixtures will
 80 be assessed. Then, a database of 59 partition coefficients of six natural compounds partitioning in
 81 eleven organic biphasic systems will be used to evaluate the COSMO-RS ability to predict partition
 82 coefficients. The influence of the parametrization TZVP or TZVPD-FINE on calculations of K_D is
 83 presented and discussed. Differences between these parametrization are the level of quantum
 84 mechanical calculations (TZVP or TZVPD basis set) and the cavity construction algorithm (FINE).[20,21]
 85 Finally, the influence of the amount of ethanol or 1-butanol in two biphasic systems containing
 86 heptane and choline chloride:levulinic acid on the partition coefficients of retinol, β -ionone and
 87 coumarin, predicted by COSMO-RS will be compared to experimental data.

88



89

90 **Fig. 1.** Structure of all compounds described in this work. A: Compounds used to prepare
 91 organic biphasic systems. B: Natural compounds used here.

92

93 2. Experimental procedure

94 2.1. Preparation of deep eutectic solvents

95 All chemicals including choline chloride (99% purity), levulinic acid (99% purity), coumarin (99% purity)
 96 , β -ionone (99% purity), retinol (95% purity) as well 1-butanol (99.4% purity), and heptane (HPLC grade)
 97 were purchased from Merck (Saint-Quentin-Fallavier, France) and were used without further
 98 purification. The structure of the compounds is presented in Fig. 1 with the compositions and
 99 abbreviations of the three DES based on choline chloride or thymol (HBA) mixed with ethylene glycol
 100 or levulinic acid (HBD) are detailed in Table 1.

101

102

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104

105 **Table 1**

106 Compositions of the five DES

107

Abbreviation	HBA	HBD	Molar ratio HBA:HBD
Ch:EG	Choline chloride	Ethylene glycol	1:2
Ch:LevA (1:2)	Choline chloride	Levulinic acid	1:2
Ch:LevA (1:3)	Choline chloride	Levulinic acid	1:3
LevA:Thym (1:1)	Levulinic acid	Thymol	1:1
LevA:Thym (1:2)	Levulinic acid	Thymol	1:2

108

109 The abbreviations used to describe the biphasic systems here studied are detailed in Table 2.

110

111 **Table 2**

112 Compositions of the seven DES-based organic biphasic systems

113

Abbreviation	Solvent 1	Solvent 2	Solvent 3
H/B/LevA	Heptane	1-Butanol	Levulinic acid
H/B/Ch:LevA (1:2)	Heptane	1-Butanol	Choline chloride - Levulinic acid (1:2)

H/B/Ch:LevA (1:3)	Heptane	1-Butanol	Choline chloride - Levulinic acid (1:3)
H/B/EG	Heptane	1-Butanol	Ethylene glycol
H/EtOAc/LevA	Heptane	Ethyl acetate	Levulinic acid
H/EtOAc/ LevA:Thym (1:1)	Heptane	Ethyl acetate	Levulinic acid - Thymol (1:1)
H/EtOAc/ LevA:Thym (1:2)	Heptane	Ethyl acetate	Levulinic acid - Thymol (1:2)

114

115

2.2 Experimental determination of the partition coefficients

116 Partition coefficients (K_D) of coumarin, β -ionone and retinol and were determined using a previously
 117 reported procedure.[19] Briefly, 2 to 3 mg of a natural compound was dissolved in 5 g of biphasic
 118 mixture. The tube was then sealed, mixed in a vortex for 1 min and left for equilibration overnight.
 119 Around 1 mL of upper and lower phases of each tube were then collected using Pasteur pipettes. Each
 120 phase was diluted 4 times in methanol and analysed by HPLC-DAD-ELSD. For each natural compound,
 121 corresponding peak surface obtained using HPLC analysis (S) is proportional to the compound
 122 concentration. Partition coefficient is calculated as a concentration ratio, and peak surface is linearly
 123 correlated to concentration. Therefore, partition coefficient, K_D is calculated starting from peak
 124 surfaces,[7] according to Eq. (1)

$$125 \quad K_D = \frac{S_{up}}{S_{low}} \quad (1)$$

126 with subscripts up and low referring to the upper and lower phases, respectively.

127

3. Modeling procedure

128 COSMO-RS was used to predict liquid-liquid equilibria (binodal curves) of organic biphasic systems and
 129 the partition coefficients of natural compounds. All thermodynamics calculations were performed
 130 using the software package COSMOtherm[22], with the BP_TZVP_21.ctd or BP_TZVPD_FINE_21.ctd
 131 parameterizations. The σ -profiles of heptane, 1-butanol, ethyl acetate, ethanol and ethylene glycol
 132 were available under parameterizations TZVP and TZVPD-FINE in the database of COSMOtherm and
 133 were used as is. The geometry and charge density of the remaining molecules were optimized using
 134 the TZVP-COSMO and TZVPD-COSMO-FINE templates included in the COSMOconf software
 135 package[23]. All calculations were performed at 25.0°C.

136 In agreement with previous studies, choline chloride was described either as a neutral pair with the
 137 chloride anion interacting simultaneously with the hydroxyl group and two methyl groups of the
 138 choline cation or as an electroneutral mixture of cholinium cation and chloride anion with or without
 139 the chloride anion solvated by one molecule of 1-butanol.[7,24,25]

140 DES were first modelled as a pseudocompound with a fixed molar ratio. This allows the DES to remain
 141 associated with both compounds partitioning in the same proportions between the two phases. In this
 142 model biphasic mixtures are considered as pseudo-ternary systems. DES were alternatively also

143 described as two independent compounds and biphasic mixture are then consider as quaternary
144 systems.

145 *3.1 Modelling of binodal curves*

146 When two immiscible liquid phases, generically α and β , are at equilibrium, the activity of each
147 component is the same in both phases:

$$148 \quad x_i^\alpha \cdot \gamma_i^\alpha = x_i^\beta \cdot \gamma_i^\beta \quad (2)$$

149 where x_i^α and x_i^β are the mole fractions of generic component i in both phases and γ_i^α and γ_i^β are the
150 corresponding activity coefficients. Thus, Equation 2 is the main criterium for liquid-liquid equilibrium.
151 For ternary systems the software package COSMOtherm uses a fine mole fraction grid to search for
152 liquid-liquid equilibrium points by evaluating the activity of each component in the system, using the
153 model COSMO-RS, and verifying if Equation (2) holds. The well-established tangent plane criterion is
154 also calculated to ensure that the Gibbs energy minima found are global, rather than local extrema.

155 For quaternary systems, the same strategy used for ternary system could be applied but the resulting
156 equilibrium point would be a four-coordinate point which cannot be represented on a ternary diagram
157 and compared to experimental data. Therefore, two different strategies were used: first quaternary
158 systems were described as pseudo-ternary systems defining a DES as a mixture of two compounds,
159 namely HBA and HBD, always remaining associated in the same phase. Alternatively, binodal points
160 were obtained using liquid extraction calculation by testing different ratio of heptane and DES with an
161 increasing amount of the third solvent and by predicting if the points are monophasic or biphasic.

162 From the experimental equilibrium points available the binodal curve was correlated using the
163 Merchuk's equation (3) to be able to interpolate and extrapolate the experimental data:

$$164 \quad w_y = A e^{(B \times w_x^D - C \times w_x^3)} \quad (3)$$

165 where w_x is the weight percentage of DES or HBD, w_y the weight percentage of heptane and A, B, C
166 and D parameters obtained by regression of equilibrium points. These adjusted parameters together
167 with the coefficient of determination (R^2) are reported in supplementary information in equations S1
168 to S9.

169 *3.2 Prediction of partition coefficients*

170 The partition coefficient of a solute at infinite dilution (K_D^0) between two immiscible liquid phases at
171 equilibrium, generically α and β , defined as the solute molar concentration ratio between phases α
172 and β , is rigorously described by the following expression:

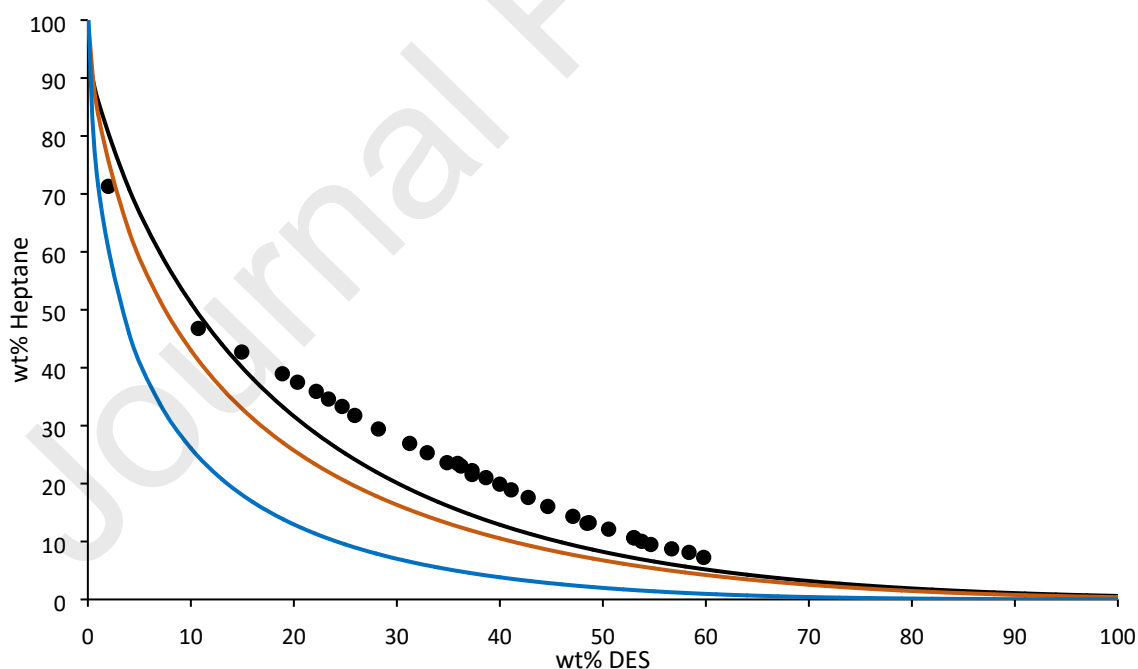
$$173 \quad K_D^0 = \exp\left(\frac{\mu_{s,\alpha}^0 - \mu_{s,\beta}^0}{RT}\right) \cdot \frac{v_\alpha}{v_\beta} \quad (4)$$

174 where $\mu_{s,\alpha}^0$ and $\mu_{s,\beta}^0$ are the infinite dilution chemical potential of the solute in phases α and β , v_α and
175 v_β are the molar volume of phases α and β , T is the absolute temperature of the system, and R is the
176 ideal gas constant. In this work, COSMO-RS was used to calculate the infinite dilution chemical
177 potential of the solutes in the immiscible phases of the organic biphasic systems studied. The
178 composition of each phase (solute-free basis) was calculated as described in the previous section. The
179 infinite dilution chemical potentials, combined with Equation 4 allowed for the estimation of the
180 partition coefficient of the solutes.

181

182 **4. Results and discussion**183 *4.1 Selection of the molecular model of choline chloride*

184 As a first step to the modelling of organic biphasic systems based on DES, the way of describing choline
185 chloride, a quaternary ammonium salt used as a HBA in DES, was studied within the framework of
186 COSMO-RS. Since its description significantly influences the calculations of thermodynamic
187 properties[26], DES were described as a mixture with a fixed composition, that is, both compounds
188 remain together and partition similarly between the polar and apolar phase. ChCl was here described
189 using three different approaches, namely as: i) a pair of ions, considering ions as fully associated; ii) as
190 a mixture of fully dissociated ions, described explicitly as separated ions; and iii) with the chloride anion
191 solvated by one 1-butanol solvent molecule. For that purpose, the influence of the choline chloride
192 description on the binodal curve of one biphasic system, namely H/B/Ch:LevA, was investigated. This
193 system was selected because the solvation of chloride anion in non-aqueous organic solvent has
194 previously been reported.[27] Only 1-butanol was expected to solvate choline chloride because
195 heptane is an apolar solvent, thus not expected to interact significantly with any ion present. Predicted
196 binodal curves for H/B/Ch:LevA using the three descriptions of choline chloride are plotted in Fig. 2
197 and compared to the experimental curve previously reported.[19] It appears that the description of
198 choline chloride as an ion pair produces the best description of the experimental data. The two other
199 descriptions led to an overestimation of the biphasic domain. These results suggest that ions probably
200 remain associated in this biphasic system, an observation in agreement with the organic nature of the
201 system. The fact that heptane and 1-butanol exhibit permittivity values of 1.9[28] and 17[29] means
202 that electrostatic interactions between ions are dominant over solvent-ion interactions, hindering the
203 solvation of chloride by 1-butanol and favoring the formation of the electroneutral ion pair. The
204 description of choline chloride as an associated ion pair was therefore selected for this study.



205 **Fig. 2.** COSMO-RS binodal curves predicted for the biphasic system H/B/Ch:LevA (1:3). Black circles:
206 Experimental data [19]. Black curve: chloride described as an ion pair. Orange curve: choline chloride
207 described as an electroneutral mixture of cholinium and chloride ions. Blue curves: choline chloride
208 described as an electroneutral mixture of cholinium cations and chloride anions solvated with one
209 molecule of 1-butanol. All calculations performed using TZVP parametrization and the DES compounds
210 as a pseudocompound.
211

212 4.2 Binodal Curve Modeling.

213 COSMO-RS predictions for binodal curves are plotted in Fig. 3 along with experimental data previously
214 reported.[19] Predictions are generally in good agreement with experimental data even though the
215 calculated biphasic domain is overestimated, particularly at low heptane and DES content. Only for the
216 system H/B/EG, COSMO-RS significantly overestimates the biphasic region. For H/B/LevA and
217 H/EtOAc/LevA, COSMO-RS was able to predict equilibrium points on the entire binodal curve with a
218 good accuracy (see supporting information). For H/B/Ch:LevA, H/B/EG and H/EtOAc/LevA:Thym ,
219 automated liquid-liquid equilibrium procedure was unable to predict equilibrium points in the vicinity
220 of the critical point, providing however a good description of the binodal away from the critical point.
221 The equilibrium points provided were sufficient to reconstitute the whole binodal curve using a
222 modified Merchuk equation.[30] In this work, the best correlation of the binodal curve was obtained
223 using a modified Merchuk equation with four adjusted parameters, as shown in eq. (3). This model
224 allowed, for all binodal curves, a very good correlation with a R^2 value above 0.990.

225 Despite the fact that adding choline chloride to a given system leads to an increase in the biphasic
226 domain, COSMO-RS predictions show no significant differences between the binodal curves of
227 H/B/LevA and H/B/Ch:LevA, for instance. Similar results had been reported for systems containing
228 ethanol instead of 1-butanol.[7]

229 The influence of thymol and of the molar ratio of levulinic acid on the binodal curves of these systems
230 were described more satisfyingly than for systems based on choline chloride. Addition of thymol to
231 levulinic acid with a molar ratio 1:1 yields a drastic decrease in the biphasic domain compared to that
232 of system H/EtOAc/LevA. In such a case, COSMO-RS predicts correctly the behavior induced by the
233 addition of thymol. Similarly, the increase in the amount of levulinic acid to a molar ratio of 1:2 leading
234 to an increase in the biphasic domain of the phase diagram is also well described by COSMO-RS.
235 Nevertheless, at first sight, binodal curves of H/B/LevA:Thym and H/EtOAc/LevA:Thym, were described
236 less accurately than homologue systems containing choline chloride.

237 In this study, all systems were described as ternary systems, with the DES described as a
238 pseudocompound. This description is satisfactory when both DES compounds are hydrophilic and
239 therefore expected to remain together in the polar phase, such as in H/B/Ch:LevA and
240 H/EtOAc/Ch:LevA . Calculated and experimental binodal curves for H/EtAc/LevA:Thym as shown in Fig.
241 3D, appear to be in relatively good agreement together. But for such a system, describing a binodal
242 curve on a pseudo-ternary diagram cannot be considered accurate because assuming DES compounds
243 remain together in the same phase when immiscibility occurs, no longer holds. Given the different
244 polarities of levulinic acid and thymol, these are expected to partition differently when two immiscible
245 phases form. This implies that for a given mixture, the molar ratio of levulinic acid vs. thymol is not the
246 same in both phases. This has been confirmed by calculations for selected H/EtOAc/LevA:Thym
247 mixtures, shown in supplementary information in Table S-16. The binodal curve is therefore not
248 expected to be located on a ternary diagram heptane/ethyl acetate/DES, but rather on a quaternary
249 diagram heptane/ethyl acetate/levulinic acid/thymol. Nevertheless, plots of the binodal curves for
250 thymol-based systems as pseudo-ternary diagrams were used in this work for comparison purposes.

251 Overall, results presented here show that the systems based on 1-butanol or ethyl acetate are
252 described better than those based on ethanol. In a previous work[7], discrepancies were observed
253 between experimental and theoretical binodal curves for systems containing heptane and ethanol that
254 were ascribed to the fact that COSMO-RS wrongly predicted a miscibility gap between these solvents.
255 In this study, COSMO-RS adequately reproduces the full miscibility of heptane with 1-butanol or ethyl
256 acetate with no biphasic mixture predicted. This is most probably due to the lower polarity differences
257 between these three solvents, as shown in Table 3. This allows a more accurate description of the
258 phase separation observed in these mixtures and of the corresponding binodal curves.

259 In an attempt to improve the description of binodal curves, molecules were described using the most
 260 detailed level of description of the surface charge of a molecule available, namely the TZVP-FINE
 261 parametrization, as opposed to TZVP previously used.[31] The binodal curves predictions using this
 262 parametrization led to a significant increase in calculation time, typically increasing from from minutes
 263 to hours. In some cases, the calculations did not converge, even after several days, and thus are not
 264 presented in this manuscript. Unexpectedly, predicted curves using TZVPD-FINE parametrization
 265 exhibit either minor differences with those obtained using the simple TZVP parametrization, such as in
 266 the case of H/B/LevA, or a larger deviation than with TZVP parametrization, as found for
 267 H/EtOAc/LevA:Thym. In the latter case, the biphasic domain overestimation is larger than that
 268 obtained with TZVP description. No improvements using TZVPD-FINE rather than

269 TZVP was therefore observed for these binodal curves predictions. This result was somewhat expected
 270 because TZVPD-FINE is the most advanced level for COSMO-RS calculations including a novel hydrogen
 271 bonding term to enhanced predictions qualities for associating mixtures.[32]

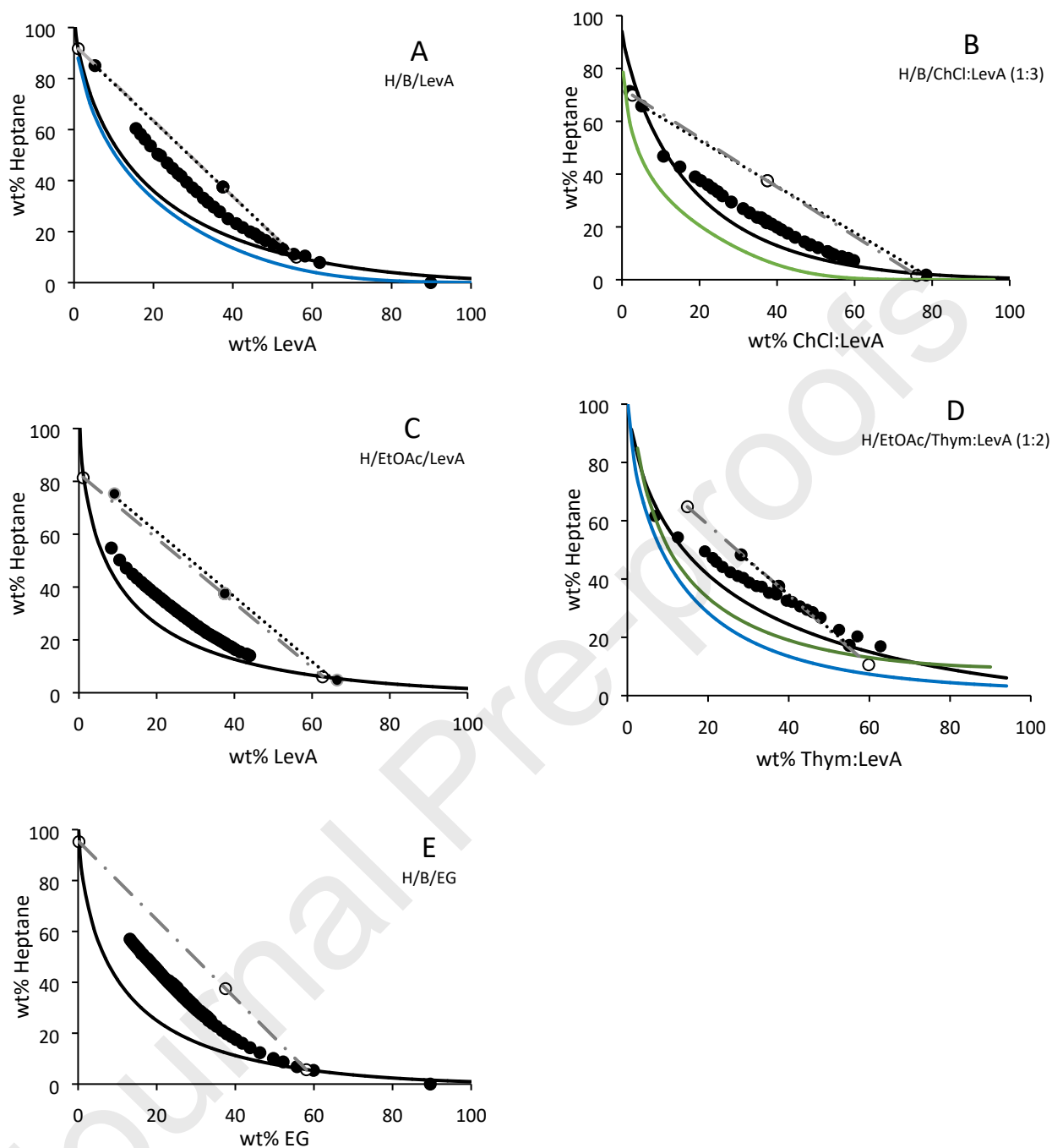
272 **Table 3**

273 Octanol–Water Partition Coefficient for the solvents in OBS

	LogK _{ow}
Heptane	4.66 ^a
Ethanol	-0.31 ^b
1-Butanol	0.88 ^b
Ethyl acetate	0.73 ^b
Levulinic acid	-0.49 ^b
Ethylene glycol	-1.36 ^b
Choline chloride	-5.16 ^c
Thymol	3.3 ^b

274

a: Ref [[33]]; b: Ref [[34]]; c: Ref [[35]]



276 **Fig. 3.** Binodal curves for biphasic systems studied here. Black circles: Experimental points taken from
 277 [[19]]. Black curve: calculations made using TZVP parametrization and both DES compounds as a fixed
 278 mixture. Green curve: calculations made using TZVP parametrization and DES compounds as
 279 separated. Blue curves: Calculations using TZVPD-FINE parametrization and DES as a fixed mixture.
 280 Dashed lines correspond to experimental tie-lines obtained starting from a mixture with a
 281 37.5/25/37.5 composition of Heptane/ Ethyl acetate or 1-Butanol/ DES or HBD. A: H/B/LevA; B:
 282 H/B/Ch:LevA (1:3); C: H/EtOAc/LevA; D: H/EtOAc/LevA:Thym (1:2); E: H/B/EG.

283 *4.3 Prediction of tie-lines.*

284 In a second step of this work, composition of immiscible phases obtained after preparing an initial
285 mixture located in the biphasic region of a phase diagram, were evaluated. Two types of biphasic
286 mixtures were selected: Systems with a fixed composition, of 37.5 wt% of heptane, 25 wt% of butanol
287 or ethyl acetate, 37.5 wt% of LevA, Ch:LevA or LevA:Thym and systems containing heptane, methanol,
288 menthol and levulinic acid previously reported in the literature.[6] Mass ratios and phase compositions
289 were calculated using COSMO-RS and compared to experimental data. Compositions for the initial
290 mixture and the resulting immiscible phases are aligned along tie-lines and are plotted in Fig. 3.
291 Calculated and experimental concentrations taken from previous references [6,19] for each compound
292 in the phases at equilibrium are presented in Tables 4 and 5.

293 It first appears that experimental and calculated tie-lines plotted in Fig. 3 are in good agreement, being
294 close form one another and intersecting the binodal curves. Only system H/EtOAc/LevA:Thym exhibits
295 a deviation between binodal curves and tie-line ends, a result in full agreement with the fact that for
296 such a system, binodal curve and tie-lines are correlated only when presented in a quaternary diagram.

297 Calculations reported in Table 4 for systems containing 1-butanol or ethyl acetate exhibit less than 10%
298 deviation from experimental data. However, heptane, which is correctly described as being
299 predominantly present in the upper apolar phase, shows the largest deviation between calculation and
300 experiment. When the second solvent is relatively apolar, such as 1-butanol and ethyl acetate, heptane
301 is overestimated in the bottom phase. Amounts of 1-butanol or ethyl acetate are calculated with an
302 overall good accuracy.

303 For systems containing choline chloride or thymol, the composition of 1-butanol or ethyl acetate is
304 overestimated in the lower phases by approximately 10%. In contrast, the composition of levulinic
305 acid, which is relatively polar and expected to be located predominantly in the lower polar phase, is
306 described with good accuracy. As explained earlier in the manuscript, thymol is expected to partition
307 between the two phases and makes it more difficult for COSMO-RS to accurately predict the phase
308 composition in H/EtOAc/LevA:Thym(1:2).

309 In general, systems with only three components are described more accurately than those with four
310 compounds, possibly due to the complexity of the solution where the occurrence of multiple
311 interactions makes it difficult for COSMO-RS to account precisely for these interactions. The largest
312 deviations in the overall phase composition are observed for the bottom phase of H/EtOAc/LevA:Thym
313 (1:3). This suggests that the phase volumes are not well described since the composition of the upper
314 phase in such a system is quite accurate.

315 Table 5 reports the calculated values for phase compositions of biphasic system containing heptane,
316 methanol, and a DES. These results show that, in the absence of methanol, the system composed of
317 heptane, menthol, and levulinic acid exhibits an upper phase mostly containing heptane, while the
318 lower phase contains the most polar compound, levulinic acid. However, COSMO-RS predictions of
319 compound partitioning in this system are less clear. Specifically, levulinic acid composition in the upper
320 phase is overestimated, resulting in an underestimation of heptane. In the lower phase, menthol is
321 overestimated, while levulinic acid is underestimated. This suggests that COSMO-RS describes
322 immiscible phases with a difference in polarity lower than expected from experimental data.

323 The addition of methanol to the system results in experimental data showing that the upper and lower
324 phases consist of heptane/menthol and methanol/levulinic acid mixtures, respectively. COSMO-RS
325 correctly predicts phase separation, but both phases contain excessive amounts of methanol and
326 levulinic acid in the upper phase, and too much heptane and menthol in the lower phase. Moreover,
327 the higher the concentration of methanol in the mixture, the larger the overestimation for the

328 concentration of heptane in the lower phase. This discrepancy is related to the model's ability to
 329 describe a miscibility gap between methanol and heptane, but with a significant overestimation of the
 330 solubility of heptane in methanol. However, increasing the amount of methanol leads to a better
 331 agreement between experimental and calculated concentrations of menthol in both phases. Regarding
 332 levulinic acid, COSMO-RS overestimates its affinity for the apolar phase. Despite the discrepancies
 333 observed in systems containing methanol, these results demonstrate that COSMO-RS is a valuable tool
 334 for predicting composition of the phases in equilibrium in complex biphasic systems.

335

336 **Table 4**

337 Phase compositions calculated using COSMO-RS for selected organic biphasic systems containing
 338 butanol or ethyl acetate. Initial mixtures has a composition of 37.5/25/37.5. Experimental data are
 339 taken from Ref. [19].

	H/B/LevA				H/B/Ch:LevA (1:3)				H/EtOAc/LevA				H/EtOAc/LevA:Thym (1:2)				Low exp.
	Up calc ·	Up exp ·	Low calc ·	Low exp ·	Up calc ·	Up exp ·	Low calc ·	Low exp ·	Up calc ·	Up exp ·	Low calc. ·	Low exp ·	Up calc. ·	Up exp ·	Low calc. ·		
Heptane /wt%	91. 7	85. 1	10. 0	11. 1	75. 7	65. 8	3.4	1.8	83. 0	75. 3	6.0	4.8	64.8	48. 3	10.6	1.8	
B or EtOAc /wt%	9.4	9.6	34. 0	33. 8	22. 0	29. 1	27. 7	19. 8	15. 9	20. 6	31.3	28. 8	20.3	23. 5	29.6	19. 8	
LevA /wt%	1.1	5.3	56. 0	55. 4	2.3	5.1	48. 6	54. 2	1.1	4.1	62.7	66. 4	3.0	9.7	17.5	24. 3	
Ch or Thy /wt%	-	-	-	-	0.0	0.0	20. 3	24. 3	-	-	-	-	11.9	18. 5	42.3	54. 2	

340

341 **Table 5**

342 Phase compositions calculated using COSMO-RS for selected organic biphasic systems containing
 343 methanol. Initial mixtures has a composition of 50 wt% of heptane and 0, 10 or 20 wt% of methanol.
 344 Experimental data are taken from Ref. [6].

H/MeOH/Menthol/LevA

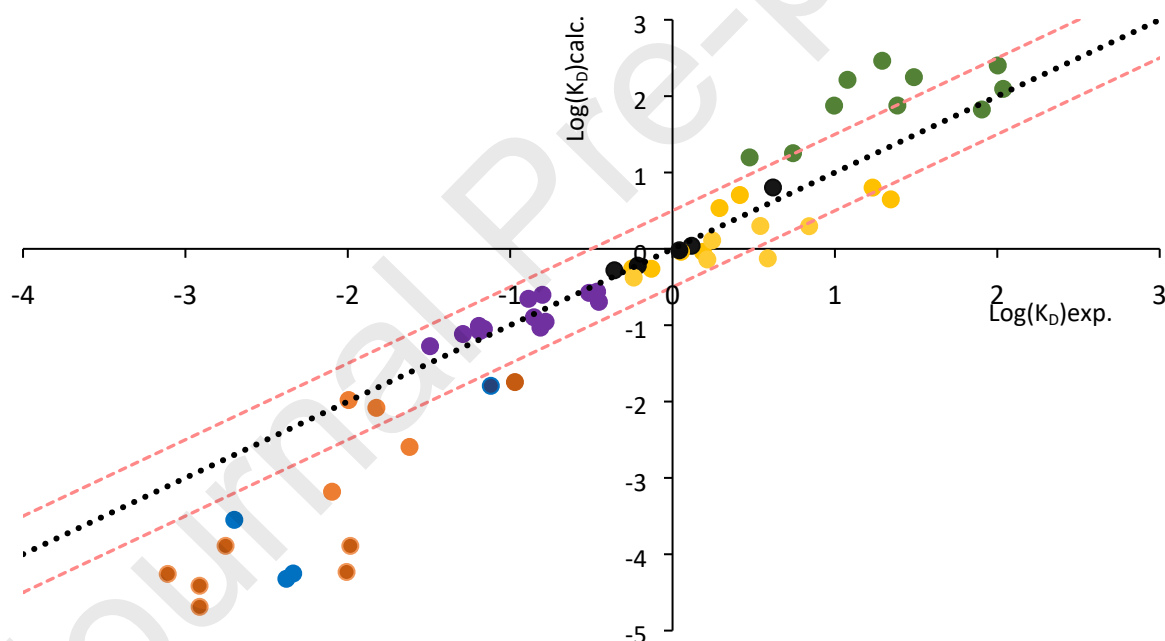
345

	50/0/29/21				50/10/23/17				50/20/17/13			
	Up calc.	Up exp.	Low calc.	Low exp.	Up calc.	Up exp.	Low calc.	Low exp.	Up calc.	Up exp.	Low calc.	Low exp.
Heptane /wt%	55.9	62.8	4.2	1.9	59.5	67.8	11.4	5.1	65.6	79.1	23.6	8.8
Methanol /wt%	-	-	-	-	6.7	3.4	18.9	26.6	12.6	2.8	32.2	44.3
Menthol /wt%	31.8	34.8	18.9	5.7	24.5	27.1	22.7	12.8	16.1	17.4	20.1	17
Levulinic acid /wt%	12.6	2.4	76.9	92.3	9.3	1.7	46.9	55.5	5.8	0.7	24.2	29.9

346

4.4 Partition of Natural Compounds.

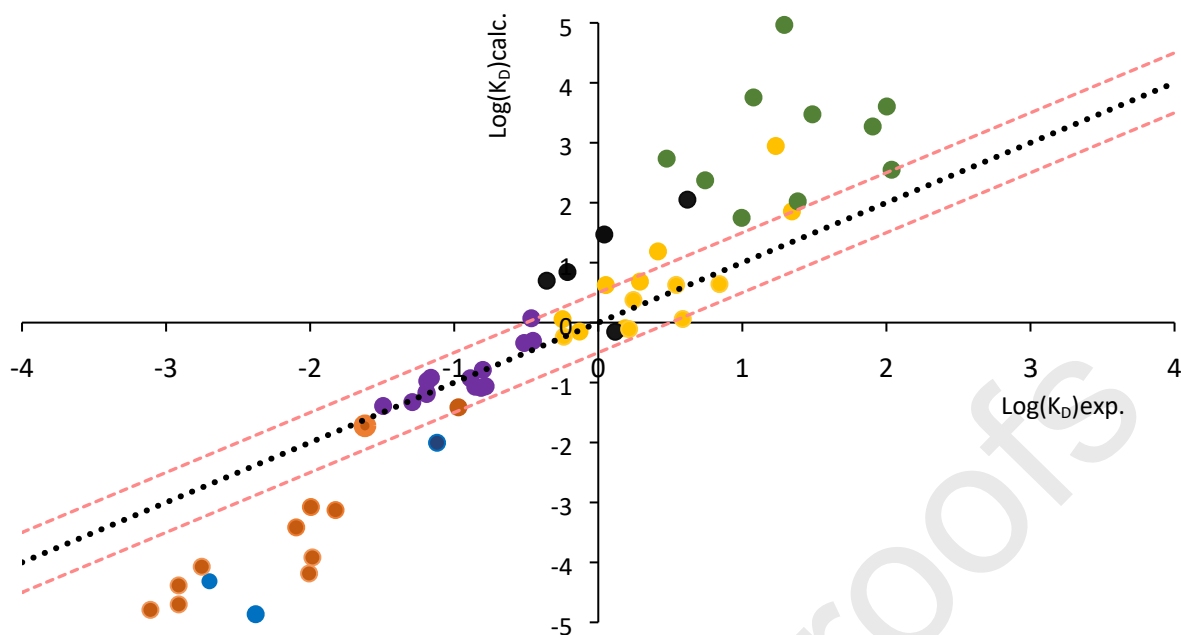
347 With the help of the composition of phases for all DES-based biphasic systems studied here, the
 348 partition at infinite dilution of six natural compounds (quercetin, coumarin, apigenin, β -ionone, retinol
 349 and α -tocopherol) were calculated and compared to experimental data from literature.[5–7,19]
 350 Natural compound were added in small amount in biphasic systems in order to measured experimental
 351 K_D values. K_D values calculated at infinite dilution and at a very low concentration, similar to those used
 352 experimentally, were found to be equivalent. In addition, calculations at infinite dilution are more
 353 straightforward than using a very low concentration of natural compound in the calculation. Therefore,
 354 experimental data were compared with data calculated at infinite dilution. Experimental and
 355 calculated values for partition coefficients are available in the supplementary information file. These
 356 molecules are representatives of three major families of compounds occurring in plants (polyphenols,
 357 terpenoids, vitamins) and are commonly used as model compounds since they cover a wide range of
 358 polarities, functional groups, structures, and bioactivities. Mixtures with composition 37.5/25/37.5 for
 359 six out of the seven biphasic systems mentioned here were used. The system H/EtOAc/LevA:Thym 1:1
 360 was excluded because the composition 37.5/25/37.5 yields a monophasic solution. Experimental and
 361 predicted values of the partition coefficients are given in supporting information (Table S-31 to S-36)
 362 and a parity plot is shown in Fig. 4 and Fig. 5 to give a overview of the prediction quality using TZVP or
 363 TZVPD-FINE parametrization for different values of the partition coefficients. Root-Mean-Square
 364 Deviations (RMSD) between experimental and predicted values are given in Table 5.



365

366 **Fig. 4.** Predicted values for the logarithm of partition coefficient of several naturel compounds as a
 367 function of experimental values taken from ref.[[19]]. Calculations carried out using TZVP
 368 parametrization. Blue points: quercetin. Orange points: apigenin. Purple points: coumarin. Yellow
 369 points: β -ionone. Black points: retinol. Green points: α -tocopherol in biphasic systems studied here.
 370 Corresponding values can be found in tables S-31 to S-36 of the supplementary file. Red dotted lines
 371 represent a difference of $\pm 0.5 \log(K_D)$ between experimental and predicted values.

372



373

374 **Fig. 5.** Predicted values for the logarithm of partition coefficient of several naturel compounds as a
 375 function of experimental values taken from ref.[19]. Calculations carried out using TZVPD-FINE
 376 parametrization. Blue points: quercetin. Orange points: apigenin. Purple points: coumarin. Yellow
 377 points: β -ionone. Black points: retinol. Green points: α -tocopherol in biphasic systems studied here.
 378 Corresponding values can be found in Table S-31 to S-36 of the supplementary file. Red dotted lines
 379 represent a difference of $\pm 0.5 \log(K_D)$ between experimental and predicted values.

380

381 **Table 6**

382 Root-Mean-Square Deviation between experimental, predicted partition coefficients, number of data
 383 points and range of $\text{Log}(K_{D-\text{exp}})$ for each group of systems.

	Overall		H/B/DES or HBD		H/EtOAc/DES or HBD		H/E/DES or HBD	
	TZVP	TZVPD-FINE	TZVP	TZVPD-FINE	TZVP	TZVPD-FINE	TZVP	TZVPD-FINE
RMSD	0,850	1,299	0,581	1,367	0,405	1,555	1,12	1,41
nbr points	59		22		10		27	
Log($K_{D-\text{Exp}}$) range	-3.1 to 2.0		-2.7 to 1.3		-1.2 to 1.3		-3.1 to 2.0	
For $-1 < \text{Log}(K_{D-\text{exp}}) < 1$ only								

RMSD	0,357 0,770	0,356 0,885	0,314 0,731	0,389 0,602
nbr points	29	13	7	9
Log(K_D-Exp) range	-1.0 to 1.0	-0.9 to 1.0	-1.0 to 0.0	-0.8 to 0.8

384

385

386 A database of almost 60 partition coefficients was used in the model evaluation. Using TZVP
 387 parametrization the partitions coefficients are generally in good agreement with experimental data. A
 388 value of 0.85 for the overall RMSD for $\text{Log}(K_D)$ is obtained. Moreover, when the experimental $\text{Log}(K_D)$
 389 values range between -1 and 1, a RMSD value of just 0.36 is obtained. Outside this range, that is when
 390 $1 < \log(K_D) < 1.5$ and $-1 > \log(K_D) > -1.5$, deviations between experimental and computed values
 391 becomes slightly more important. These predicted values are however still acceptable with a RMSD
 392 value of 0.60 for 13 data points. However, COSMO-RS failed to properly predict values for $\text{Log}(K_D)$
 393 above 1.5 or below -1.5 (RMSD= 1.42).

394 This inaccurate description of high partition coefficient values by COSMO-RS is nevertheless not
 395 critical. A value for $\text{Log}(K_D)$ above 1.5 implies that a compound partitions almost quantitatively to one
 396 phase, since it corresponds to 97% of a compound partitioning to the upper phase. This implies that
 397 the concentration of natural compounds in one of the phases is very small compared to that in the
 398 other phase. Therefore, even a small prediction error of these concentrations can lead to a significant
 399 deviation on the partition coefficient value.

400 These results imply that COSMO-RS describes well compounds that interact with both phases, but
 401 somehow underpredicts the partition coefficients of compounds that partition extensively towards
 402 one phase. In the case of application of such biphasic systems to the purification of natural compounds
 403 using CPC, the most adequate values for $\log(K_D)$ are expected to range between -0.3 and 0.4 where
 404 COSMO-RS seems to provide accurate predictions.

405 For systems containing heptane and a specific DES, and either ethanol, ethyl acetate or 1-butanol,
 406 accordingly, RMSD values of 1.13, 0.59 or 0.40, are obtained respectively. This reveals that higher
 407 deviations between calculated and experimental data are obtained in presence of ethanol. This result
 408 is most probably due to the inaccurate description of heptane and ethanol miscibility by COSMO-RS,
 409 as discussed earlier.

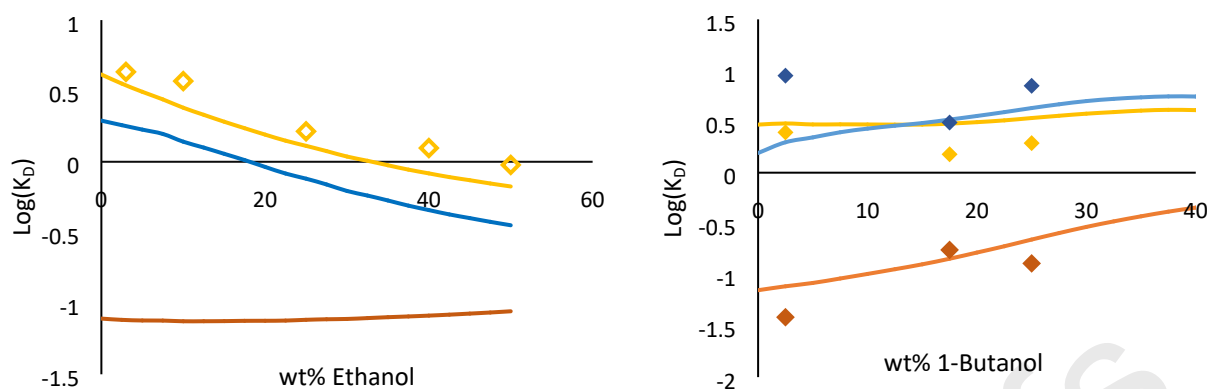
410 The use of TZVPD-FINE parametrization did not improve the predictions of partition coefficients.
 411 Unexpectedly, this second parametrization led to larger deviations between experimental and
 412 predicted values, with an overall RMSD value of 1.55 and a value of 0.77 when $\text{Log}(K_D)$ values ranging
 413 between -1 and 1 are taken into account. The better performance of TZVP could be due to different
 414 interaction terms or the parameter sets. Discuss and find the specific reasons for these results is then
 415 tedious and not straightforward.

416 To design systems for the purification of natural compounds, it is important to be able to adequately
 417 describe the influence of the concentration of a given solvent, such as heptane, 1-butanol or ethyl
 418 acetate. Experimentally, these studies are very time consuming, but using a model the assessment of

419 the solvent effect can be carried out quickly. In this study, the partition coefficients of apigenin,
420 coumarin, ionone and retinol in systems H/B/Ch:LevA(1:3) and on H/E/Ch:LevA(1:2) containing equal
421 amount of heptane and DES and varying concentrations of ethanol or 1-butanol from 0 to 50 wt%,
422 were calculated. All mixtures modelled here are biphasic, in agreement with the phases diagrams
423 shown in Fig. 3. The results are presented in Fig. 6. For comparison, the experimental data available
424 [5] are also plotted.

425

Journal Pre-proofs



426

427 **Fig. 6.** Values for the partition coefficients of β -Ionone, retinol and coumarin in systems
 428 H/E/Ch:LevA(1:2) and on H/B/Ch:LevA(1:3) varying concentrations of ethanol and 1-butanol,
 429 accordingly. For all compositions the amount of DES was keep equal to the amount of heptane. Open
 430 symbols: experimental data for β -Ionone taken from Ref [5]. Full symbols: experimental data from this
 431 study. Lines: COSMO-RS predictions - Yellow: β -Ionone; Blue: Retinol; Orange: Coumarin

432

433 The results of this study indicate that the partition coefficients (K_D) of β -Ionone and Retinol in the
 434 H/E/Ch:LevA(1:2) system decrease as the concentration of ethanol increases. In contrast, in the
 435 H/B/Ch:LevA(1:3) system, the same compounds exhibit an increasing trend of K_D values with the
 436 percentage of 1-butanol. Experimental data for β -Ionone in the H/E/Ch:LevA[5] system are plotted in
 437 Fig. 6, showing that the predicted values agree well with the experimental ones, albeit slightly
 438 underestimating the partition coefficients. Overall, the COSMO-RS model provides a satisfactory
 439 description of the observed decreasing trend of K_D values in the presence of ethanol, as the decreasing
 440 polarity of the lower phase leads to a higher retention of apolar compounds in the lower phase.
 441 Conversely, the higher concentration of 1-butanol in the top phase of the H/B/Ch:LevA system reduces
 442 the polarity of this phase and favors the partitioning of these compounds from the lower to the upper
 443 phase. The study of the phases compositions confirms that ethanol mainly partitions to the lower
 444 phase of the H/E/Ch:LevA system, while 1-butanol is more concentrated in the upper phase of the
 445 H/B/Ch:LevA system. This difference in polarity and distribution of the solvents explains the opposite
 446 trends of K_D values for β -Ionone and Retinol in the two systems.

447 5. Conclusion

448 COSMO-RS has proven to be effective in predicting both phase diagrams of DES-based OBS and
 449 partition coefficients of natural compounds in these systems. The present study employed COSMO-RS
 450 to describe systems composed of heptane + ethyl acetate or 1-butanol + ethylene glycol, levulinic acid,
 451 or the corresponding choline chloride or thymol-based DES. Predicted binodal curves were in good
 452 agreement with experimental data measured by cloud point titration, although COSMO-RS was unable
 453 to predict the binodal curve around the critical region in some cases.

454 The best description of the experimental data was obtained when choline chloride was dealt as an ion
 455 pair rather than an electroneutral mixture with or without chloride solvation. Partition coefficients
 456 were calculated for six natural compounds representing different chemical families and exhibiting
 457 different polarities, and these were compared to experimental data. The overall RMSD value was 0.83,
 458 which was satisfactory. When logarithmic values for the partition coefficients ranged between -1 and
 459 1, the deviation between predicted and experimental values was low, with an RMSD value of 0.36.
 460 Thus, COSMO-RS appears to be an accurate model for predicting partition coefficients when

461 compounds are found at concentrations of the same order of magnitude in both phases. . Additionally,
462 COSMO-RS was used to describe the influence of the amount of ethanol or 1-butanol on the partition
463 of four natural compounds. The calculations were in agreement with the experimental data available
464 in the literature.

465 However, some limitations were also identified. Experimentally, adding choline chloride to a given
466 system was found to lead to an increase in biphasic domain. COSMO-RS was however not able to
467 predict this effect of ChCl and showed no significant differences between binodal curves for H/B/LevA
468 and H/B/Ch:LevA, for instance. No improvement was observed for these binodal curves or partition
469 coefficient of natural compounds in these systems when using TZVPD-FINE rather than BTZVP
470 parametrization. In general, systems with only three components are described more accurately than
471 those with four compounds, and systems containing methanol were not accurately described by
472 COSMO-RS. On the latter an overestimation of the affinity of methanol for the apolar phase was
473 observed. Despite these limitations, this work establishes COSMO-RS as a valuable tool for the design
474 of organic biphasic systems to be used in the purification of natural compounds.

475

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481

482 CrediT authorship contribution statement

483 **Jean-Baptiste Chagnoleau:** Investigation, Writing – original draft. **Nicolas Papaiconomou:**
484 Conceptualization, Supervision, Validation, Writing – review & editing. **Xavier Fernandez:** Supervision,
485 Writing – review & editing. **Joao A.P. Coutinho:** Conceptualization, Supervision, Validation, Project
486 administration, Writing – review & editing.

487

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593 **Highlights**

594 COSMO-RS was used to predict properties of organic biphasic systems containing deep eutectic
595 solvents.

596 Biphasic systems studied theoretically aim to be applied to the separation of natural compounds.

597 COSMO-RS predicted well binodal curves and phase compositions of 4 components DES-based
598 biphasic systems.

599 Good prediction of partition coefficients were obtained for natural compounds in DES-based
600 systems.

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603

604 **CrediT authorship contribution statement**

605 **Jean-Baptiste Chagnoleau:** Investigation, Writing – original draft. **Nicolas Papaiconomou:**
606 Conceptualization, Supervision, Validation, Writing – review & editing. **Xavier Fernandez:** Supervision,
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