

# Octanol–Water Partition Coefficients and Aqueous Solubility Data of Monoterpenoids: Experimental, Modeling, and Environmental Distribution

Sérgio M. Vilas-Boas, Mariana C. da Costa, João A. P. Coutinho, Olga Ferreira,\* and Simão P. Pinho\*



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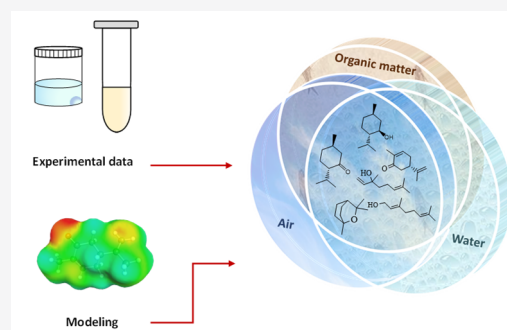


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**ABSTRACT:** Terpenes and terpenoids encompass one of the most extensive and valuable classes of secondary metabolites. Their ten-carbon-containing oxygenated representatives, monoterpenoids, are the main components of plant essential oils, being widely exploited in the cosmetic, pharmaceutical, and food industrial areas. Due to its widespread use, it is crucial to investigate their environmental distribution. Thus, new water solubility data were obtained for six monoterpenoids ((1R)-(+)-camphor, (S)-(+)-carvone, eucalyptol, (1R)-(-)-fenchone, L-(-)-menthol, and (-)-menthone) at 298.2 and 313.2 K. Furthermore, octanol–water partition coefficients of 12 monoterpenoids (the six mentioned above plus carvacrol, ( $\pm$ )- $\beta$ -citronellol, eugenol, geraniol, linalool, and thymol) were measured at 298.2 K. The COSMO-RS thermodynamic model and other more empirical approaches were evaluated for the description of the solubilities and partition coefficients, showing reliable predictions. Lastly, the distribution of the monoterpenoids in the different environmental compartments was assessed through an intuitive two-dimensional chemical space diagram based on the physicochemical equilibrium information reported.



## 1. INTRODUCTION

Terpenes and terpenoids comprise the largest and the most structurally diverse class of compounds produced by plants,<sup>1,2</sup> currently covering more than 80,000 identified substances.<sup>3</sup> Despite their large structural variety, these compounds are derived from the same 5-carbon precursor, the isoprene molecule.<sup>3,4</sup> The term terpene usually refers to hydrocarbons, whereas terpenoid is applied for modified terpenes, typically those with oxygen-containing functional groups.<sup>2</sup> Due to their large chemical diversity, terpenes and terpenoids are employed in several industrial fields, such as fragrances,<sup>5,6</sup> therapeutical and pharmaceutical products,<sup>7–10</sup> food additives,<sup>11,12</sup> polymers,<sup>13–15</sup> fine chemicals precursors,<sup>16–18</sup> and biofuels.<sup>19</sup>

Monoterpenes and monoterpenoids are short-chain terpene representatives constituted by ten carbon backbone structures, being the major components of essential oils.<sup>20,21</sup> They exhibit diverse biological activities,<sup>21</sup> some being proposed for the topical treatment of chronic pain.<sup>22</sup> Besides, monoterpenoids are widely used in the cosmetic industry due to their typical pleasant aroma and intrinsic lipophilic nature, facilitating their skin penetration.<sup>22</sup> Some of the most common monoterpenoids are linalool, geraniol, carvone, thymol, menthol, eucalyptol, and camphor, whereas limonene, myrcene,  $\alpha$ -pinene, and  $\beta$ -pinene are relevant representatives of the monoterpene group.<sup>20,23</sup>

Despite their vast range of unique applications, monoterpenes and monoterpenoids comprise a significant fraction of

biogenic volatile organic compound (VOC) emissions by the terrestrial and marine biosphere.<sup>24,25</sup> These compounds are reactive with ozone and other oxidants present in the troposphere, producing gas- and particle-phase compounds that affect atmospheric composition and radiation balance.<sup>24–26</sup> Moreover, the presence of VOCs in the atmosphere is also related to the formation of secondary organic aerosols (SOAs), which strongly interfere in the radiation balance and the cloud microphysics.<sup>25,27</sup> Besides, there is evidence that monoterpenes and their oxygenated derivatives might inhibit many ecological processes, such as nitrification, methane oxidation, and saprotrophic fungal activity.<sup>28</sup> In this context, the vapor pressure of monoterpenoids and their solubility in water and octanol–water partition coefficients are crucial properties for monitoring their distribution and fate in the different environmental compartments.<sup>29–32</sup> These last two properties also play a crucial role in understanding diffusion-related biological processes<sup>33</sup> and in the design of controlled-release drug delivery systems.<sup>34</sup> In addition, the knowledge of the octanol–water partition coefficients might provide some

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
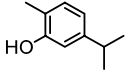
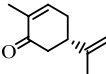
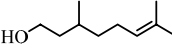

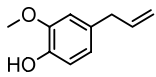
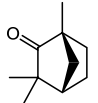
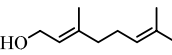
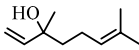
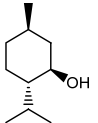
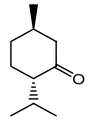
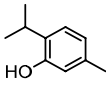

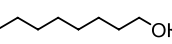
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Table 1. Purity (Mass %), Chemical Structure, CAS Number, and Source of the Compounds Used in This Work

Compound	CAS	structure	source	purity (mass %) <sup>a</sup>	melting point (K)
(1R)-(+)-camphor	464-49-3		Aldrich	≥ 98	451 ± 2 <sup>57</sup>
carvacrol	499-75-2		Acros	≥ 97.5	276.65 <sup>58</sup>
(S)-(+)-carvone	2244-16-8		Merck	≥ 98	246.7 ± 0.3 <sup>59</sup>
(±)-β-citronellol	106-22-9		Aldrich	≥ 95	< 253.15 <sup>c</sup>
eucalyptol	470-82-6		Aldrich	≥ 99	274.1 ± 0.3 <sup>60</sup>
eugenol	97-53-0		Aldrich	≥ 99	261.8 ± 0.3 <sup>59</sup>
(1R)-(-)-fenchone	7787-20-4		Aldrich	≥ 98	278.6 ± 0.3 <sup>61b</sup>
geraniol	106-24-1		Aldrich	≥ 98	258.15 <sup>c</sup>
linalool	78-70-6		Aldrich	≥ 97	< 248.15 <sup>d</sup>
L-(-)-menthol	2216-51-5		Acros	≥ 99.5	315.6 ± 0.02 <sup>62</sup>
(-)-menthone	14073-97-3		Fluka	≥ 90	264.0 ± 0.7 <sup>63</sup>
thymol	89-83-8		TCI	≥ 99	322.0 ± 0.1 <sup>64</sup>
toluene	108-88-3		Fisher	≥ 99	178.15 ± 0.05 <sup>65</sup>
1-octanol	111-87-5		Carlo Erba	≥ 99	258.43 ± 0.02 <sup>66</sup>

<sup>a</sup>The values correspond to the minimum purities granted by the manufacturer. <sup>b</sup>Data for (+)-fenchone. <sup>c</sup>Reported by Alfa Aesar. <sup>d</sup>Available in Chemspider.<sup>68,69</sup>

clues about the fate of organic solutes in contaminated terrestrial and aquatic environments.<sup>35,36</sup> Nevertheless, vapor pressure, solubility, and octanol–water partition coefficients available in the literature are scarce and often highly

inconsistent.<sup>37</sup> A critical assessment of the retrieved information is still needed.

In previous work from our group,<sup>38</sup> the solubility of carvacrol, (±)-β-citronellol, eugenol, geraniol, linalool, and thymol in water was determined between 298.2 and 323.2 K.

The present study reports the aqueous solubilities of (1R)-(+)-camphor, (S)-(+)-carvone, eucalyptol, (1R)-(-)-fenchone, L-(-)-menthol, and (-)-menthone measured at 298.2 and 313.2 K and the octanol–water partition coefficients ( $K_{ow}$ 's) of all monoterpenoids mentioned above at 298.2 K. A comprehensive literature review of experimental aqueous solubilities and  $K_{ow}$ 's available for the selected solutes was carried out, and the retrieved data were critically compared to those obtained in this work.

Although experimental methods are usually preferred to obtain reliable physicochemical properties, accurate solubility and octanol–water partition coefficient measurements of hydrophobic solutes are typically costly and time-consuming.<sup>39,40</sup> A feasible alternative is the use of theoretical and empirical thermodynamic models to estimate these key physicochemical attributes. In this work, the COSMO-RS model,<sup>41–43</sup> the Abraham solvation model,<sup>44–46</sup> and the ACD/Log  $P$  add-on for the ACD/Chemsketch 2019.1.2 freeware package<sup>47,48</sup> were employed to estimate the  $K_{ow}$  of the 12 monoterpenoids being studied. The COSMO-RS model and the Abraham solvation method were already successfully applied to predict the log  $K_{ow}$  of several terpenes and terpenoids,<sup>49–54</sup> whereas the ACD/Log  $P$  is a fragmental method often used by chemists and a fast screener of the log  $K_{ow}$  predictions. In the case of COSMO-RS, one particular study,<sup>52</sup> in which the authors evaluated the model to describe the octanol–water partition coefficients of 11 small drug-like molecules proposed by the SAMPL6 blind challenge, deserves to be noted. In this work, the authors predicted the  $K_{ow}$  of the proposed molecules without having access to the experimental data, and COSMO-RS presented the lowest root-mean-square deviations (RMSDs) from 91 submissions to the competition. Due to its *a priori* nature, COSMO-RS was also used to describe the aqueous solubilities of the monoterpenoids being studied,<sup>55</sup> and the results were compared with the estimations provided by simpler predictive models (General Solubility Equation and EPI Suite WSKOWin).

Following a straightforward qualitative approach,<sup>56</sup> the equilibrium data obtained in this work, and vapor pressures collected from the open literature, are used to screen the persistence of the terpenoids once released in the environment. The compartments are, in this method, modeled as volumes of air, water, and octanol, the latter representing the organic portion from soils and sediments. The use of an environment space diagram shows their probable environmental distribution.

## 2. EXPERIMENTAL SECTION

**2.1. Chemicals.** The structure, source, purity, and melting points of the organic compounds used in this work are listed in Table 1. Water from ultrapure quality (resistivity of 18.2 M $\Omega$ .cm, free particles  $\geq 0.22 \mu\text{m}$ , and total organic carbon  $< 5 \mu\text{g dm}^{-3}$ ) was used in the solubility and partition coefficient experiments. All the selected monoterpenoids were used as received from the supplier.

**2.2. Measurement of Partition Coefficient.** The octanol–water partition coefficients were measured using the traditional shake-flask method, explained in detail elsewhere.<sup>70,71</sup> To prevent any micelle formation, octanol presaturated with water (5% on a volume basis), or water presaturated with octanol, was initially prepared and stored. Briefly, a sample between 5 and 40 mg (ABT 100-5M, Kern,  $\pm 0.01$  mg) of solute was dissolved in 7 mL of water-saturated

octanol before being transferred to an all-glass graduated tube along with 7 mL of octanol-saturated water. As suggested by Leo and coauthors,<sup>72</sup> the tubes were repeatedly inverted around 100 times at room temperature to facilitate the distribution of the solute in both phases. Then, the tubes were placed in an Eppendorf ThermoMixer C at  $298.2 \pm 0.5$  K under continuous stirring (300 rpm) for 6 h, followed by at least 15 h of settling. Afterward, the tubes were centrifuged at 1500 rpm, at  $298.2 \pm 2$  K, for 40 min (5800 series, Eppendorf) followed by a settling period of at least 1 h in the Thermomixer before sampling. To ensure reliability, at least two independent samples were prepared, and polypropylene syringes were used to collect three samples ( $0.2\text{--}3 \text{ cm}^3$ ) from both phases to be analyzed employing UV–vis spectroscopy or GC analysis. Details of the analytical procedures are presented in section SM1 and Table S1 of the Supporting Information.

**2.3. Solubility Measurements.** The solubility experiments were carried out using the isothermal shake-flask method as described in previous works from our group.<sup>73–75</sup> Briefly, a slight excess of solute was mixed with around  $80 \text{ cm}^3$  of ultrapure water. Stirring was promoted by magnetic stirrers (Cimarec I micro stirrer, ThermoFisher) inside a heated circulating bath (TC120, Grant) equipped with a temperature control system ( $\pm 0.1$  K). Preliminary tests showed that 72 h of continuous agitation (500 rpm, standard Telemodule controller, Thermo Fisher Scientific) followed by 24 h of settling was sufficient to reach equilibrium. For each terpenoid, two independent saturated solutions were prepared. The samples, between  $0.2$  and  $0.5 \text{ cm}^3$ , were collected using preheated polypropylene syringes, coupled with hydrophilic filters ( $0.45 \mu\text{m}$  pore diameter) in the case of solid solutes. Afterward, the quantification was carried out by GC using the same procedure detailed in section SM1. The reported solubility values are the average of at least six independent measurements. To validate the experimental methodology, the solubilities of linalool and toluene were measured at 298.2 K, using GC and UV–vis analysis, respectively.

## 3. MODELING

**3.1. Thermodynamic Framework.** The octanol–water partition coefficient of a nonelectrolyte organic solute  $i$ , when the solute is at infinite dilution in both phases, can be expressed as<sup>76</sup>

$$K_{ow} = \frac{C_I^{octanol, \infty}}{C_I^{water, \infty}} \quad (1)$$

where  $C_I$  corresponds to the molar concentration of compound  $I$ , the subscript  $\infty$  stands for the infinite dilution state, and the *octanol* and *water* superscripts stand for the octanol-rich and water-rich phases. Alternatively, the  $K_{ow}$  of component  $I$  can be calculated from the activity coefficient at infinite dilution ( $\gamma_I^\infty$ ) and the molar volume ( $v$ ):

$$K_{ow} = \frac{\gamma_I^{water, \infty} \cdot v^{water}}{\gamma_I^{octanol, \infty} \cdot v^{octanol}} \quad (2)$$

In this work, the experimental  $K_{ow}$  was calculated through eq 1, whereas eq 2 was applied to predict the partition coefficients with COSMO-RS.

The solubility of a solid compound ( $i$ ) in a liquid, under some assumptions, can be described by<sup>77</sup>

$$\ln(x_i \gamma_i) = \frac{\Delta_m H_i}{R} \left( \frac{1}{T_{m,i}} - \frac{1}{T} \right) + \frac{\Delta_m C_{p,i}}{R} \left( \frac{T_{m,i}}{T} - \ln \frac{T_{m,i}}{T} - 1 \right) \quad (3)$$

in which  $x$  and  $\gamma$  are the mole fraction solubility and the activity coefficient of component  $i$ , respectively,  $\Delta_m H$  is the melting enthalpy,  $T_m$  is its melting point,  $\Delta_m C_p$  is its heat capacity change upon fusion,  $T$  is the absolute temperature, and  $R$  is the ideal gas constant. Since the heat capacity change upon melting is often unavailable and often has a negligible impact on the equilibrium calculations, the heat capacity term in eq 3 can be neglected, resulting in

$$\ln(x_i \gamma_i) = \frac{\Delta_m H_i}{R} \left( \frac{1}{T_{m,i}} - \frac{1}{T} \right) \quad (4)$$

In this work, eq 4 was applied to describe the aqueous solubility of the terpenes that are solid in the studied temperature range ((1R)-(+)-camphor, L-(-)-menthol, and thymol) with the COSMO-RS model. To compute the solubility data, experimental melting temperatures and enthalpies of these solutes were collected in the literature<sup>57,64,78</sup> and are presented in Table S2 of section SM2.

**3.2. COSMO-RS Model.** The COSMO-RS model is a well-established quantum chemistry-based statistical thermodynamic approach, able to efficiently predict several thermophysical properties of liquid mixtures and fluids.<sup>79,80</sup> A comprehensive description of the fundamental concepts is available elsewhere.<sup>41–43,52,55,81</sup> Briefly, the model assumes that the solute molecules are immersed in a virtual conductor environment. All the intermolecular interactions occur on the molecule-conductor interface, being described as pairwise contacts of the component surface segments.<sup>41,52</sup> In contrast to most of the group contribution and hybrid methods, which typically require at least some amount of experimental data, COSMO-RS needs only the structure, electronic energy, and polarization charge density ( $\sigma$ ) of each component to compute the chemical potential of the compounds.

The simulations were carried out with the COSMOtherm software<sup>82</sup> with the BP\_TZVP\_21.ctd parametrization. The required input files containing the electronic energy and  $\sigma$ -profiles for each monoterpene were generated using the TmoleX software package<sup>83</sup> using the COSMO-BP-TZVP user template, considering a def-TZVP basis set combined with the density theory level (utilizing the B-P86 functional level of theory and the COSMO solvation model). The water and octanol structural information was taken from the COSMOtherm TZVP database. The  $\sigma$ -profiles generated for the solutes, water, and octanol are presented in Figure S1 of section SM2 of the Supporting Information.

**3.3. Abraham Solvation Model.** The Abraham solvation model correlates the water–solvent partition coefficient of a series of nonelectrolyte solutes in a given solvent system (in molar concentration basis) by the following linear free energy relationship (LFER)<sup>44,45</sup>

$$\log P = \frac{C_s}{C_w} = c + eE + sS + aA + bB + vV \quad (5)$$

in which  $C_s$  and  $C_w$  correspond to the molar concentration of the solute in the organic solvent-rich phase and in the aqueous phase, respectively; the lowercase parameters ( $c$ ,  $e$ ,  $s$ ,  $a$ ,  $b$ ,  $v$ ) refer to the model solvent descriptors, available in the literature for a series of biphasic systems,<sup>45,84,85</sup> the solute descriptors are represented by the uppercase parameters ( $E$ ,  $S$ ,  $A$ ,  $B$ ,  $V$ ), where

$E$  is the solute excess molar refractivity,  $S$  stands for the solute dipolarity/polarizability,  $A$  and  $B$  account for the overall solute hydrogen bond acidity and basicity, and  $V$  is the solute's McGowan characteristic molecular volume.<sup>86</sup>

To estimate the octanol–water partition coefficients with the Abraham solvation model, the solute and solvent descriptors were retrieved from the open literature<sup>49,84,87,88</sup> and are presented in Tables S3 and S4 of section SM2.

**3.4. ACD/Log P Approach.** The ACD/Log P is a pure fragmental method that considers structural correction factors in the calculations of the octanol–water partition coefficients.<sup>48</sup> In this method, the fragmentation rules are based on the definition of isolating carbon, which cannot form double or triple bonds with a heteroatom. As discussed by Petrauskas and Kolovanov,<sup>48</sup> the ACD/Log P model provided better  $\log K_{ow}$  estimations for a set of 48 drugs than other fragmental-based and atom-based models, though it presents a more significant number of individual increments, mainly to describe the aromatic interactions, than the other models. Since the ACD/Log P add-on is a free, widespread, and straightforward method to perform fast  $\log K_{ow}$  predictions, requiring only the solute's chemical structure, this model was also selected to describe the partitions studied in this work.

**3.5. General Solubility Equation (GSE).** The GSE is a very simple and elegant expression that correlates the solubility of a crystalline, nonelectrolyte solute with its melting point and octanol–water partition coefficient as follows<sup>89,90</sup>

$$\log S_w^{solid} = 0.5 - 0.01(\text{mp} - 25) - \log K_{ow} \quad (6)$$

where  $S_w^{solid}$  is the solubility of the solute (in molar concentration basis), and mp is the solute melting point (in °C). The derivation of this equation was based on the following assumptions: a) the solvent presence does not affect the crystallinity of the solute; b) the constant entropy of melting given by Walden's rule is considered for the nonelectrolyte solutes; c) the solid–liquid heat capacity effects are negligible on the calculation of the solubility; d) the solute octanol–water partition coefficient is equal to the ratio of its solubility in octanol and its solubility in water; and e) the solute is fully miscible with octanol.

In the case of liquid solutes, the water solubility is expressed by the following simplified form of the GSE:

$$\log S_w^{liquid} = 0.5 - \log K_{ow} \quad (7)$$

To describe the solubility data of the monoterpenoids with the GSE approach, the experimental octanol–water partition coefficients obtained in this work were used. In the case of the monoterpenoids that are solid at room temperature, the melting temperatures presented in Table S2 of the Supporting Information were also considered.

**3.6. EPI Suite.** EPI Suite is a compilation of individual models to estimate organic compounds' physicochemical properties and risk assessment.<sup>91</sup> Among its several methods, the EPI Suite WATERNT v1.01 module is a predictive tool designed to estimate water solubilities based on a fragmental approach.<sup>91,92</sup> Due to its simplicity, free availability, and evidenced capacity to deliver reasonable water-solubility predictions of organic solutes,<sup>92–94</sup> this model was also selected to describe the solubility data of the studied monoterpenoids at 298.2 K.



## 4. RESULTS AND DISCUSSION

**4.1. Experimental Octanol–Water Partition Coefficients.** The experimental partition coefficients obtained in this work for (1*R*)-(+)-camphor, carvacrol, (*S*)-(+)-carvone, ( $\pm$ )- $\beta$ -citronellol, eucalyptol, eugenol, (1*R*)-(-)-fenchone, geraniol, linalool, *L*-(-)-menthol, (-)-menthone, thymol, and toluene (reference compound) are presented in Table 2 along

**Table 2. Octanol–Water Partition Coefficients of the Studied Monoterpenoids Measured at 298.2 K in This Work and Average from the Literature**

monoterpenoid	$\log K_{ow,exp}^a$	$\log K_{ow,lit}^b$
(1 <i>R</i> )-(+)-camphor	2.41 $\pm$ 0.02	2.56 $\pm$ 0.44
carvacrol	2.99 $\pm$ 0.08	3.46 $\pm$ 0.25
( <i>S</i> )-(+)-carvone	2.47 $\pm$ 0.06	2.93 $\pm$ 0.13
( $\pm$ )- $\beta$ -citronellol	3.21 $\pm$ 0.01	3.78 $\pm$ 0.29
eucalyptol	2.89 $\pm$ 0.02	2.91 $\pm$ 0.44
eugenol	2.23 $\pm$ 0.07	2.29 $\pm$ 0.02
(1 <i>R</i> )-(-)-fenchone	2.59 $\pm$ 0.01	3.12 $\pm$ 0.40
geraniol	2.54 $\pm$ 0.03	3.15 $\pm$ 0.63
linalool	3.19 $\pm$ 0.03	3.02 $\pm$ 0.34
<i>L</i> -(-)-menthol	3.85 $\pm$ 0.11	3.32 $\pm$ 0.09
(-)-menthone	3.33 $\pm$ 0.14	3.13 $\pm$ 0.08
thymol	3.15 $\pm$ 0.09	3.35 $\pm$ 0.13
toluene	2.50 $\pm$ 0.09	2.56 $\pm$ 0.18

<sup>a</sup>Data from this work.  $u(T) = 2$  K and  $u_r(p) = 0.05$ . Standard deviations are placed after the plus-minus sign. <sup>b</sup>Average value of the experimental  $\log K_{ow}$  available in the literature. Overall standard deviations are placed after the plus-minus sign.

with the average  $\log K_{ow}$  calculated from data found in the open literature. All the partition coefficients considered in the calculation of the average values, and the experimental methodology used, are summarized in Table S5 of section SM3, together with some comparative analysis.

The coefficients of variation, always inferior to 4.3%, show an excellent consistency between the results measured in this work. Additionally, the mass of solute distributed in each phase was retrieved by material balance and compared with the weighted values, showing average relative deviations (ARDs%) always below 5%. The octanol–water partition coefficient for toluene was also measured to validate the experimental procedure. The  $\log K_{ow}$  value (2.50  $\pm$  0.09) here obtained agrees with the literature average (2.56  $\pm$  0.18) measured by the shake-flask method or by reversed-phase high-performance liquid chromatography (RP-HPLC), both recommended by the OECD<sup>71,95</sup> as suitable methods for the determination of reliable  $\log K_{ow}$  data. This solute was chosen as a reference compound due to its strong hydrophobic nature and  $\log K_{ow}$  of the same magnitude as of the studied monoterpenoids. The  $\log K_{ow}$  obtained for toluene is in high agreement with the average literature data, also supporting the methodology proposed, showing its suitability to measure  $K_{ow}$ .

The measured  $\log K_{ow}$  varied from 2.23 (eugenol) to 3.85 (*L*-(-)-menthol), which is the most hydrophobic solute. Except for linalool, *L*-(-)-menthol, and (-)-menthone, the  $\log K_{ow}$  measured in this work is systematically lower than the literature average, but a large variability is observed. That confirms that the determination of reproducible octanol–water partition coefficients remains a challenge. It is worth mentioning that solute concentrations lower than 0.01 M in both octanol-rich and water-rich phases are desirable for

accurate partition coefficient measurements,<sup>71,72</sup> ensuring that the solute is close to the infinite dilution state.<sup>96</sup> At higher concentrations, the solute–solute interactions might be substantial, affecting the overall solute distribution between the two phases. Nevertheless, no comments about this precaution were found in most of the papers mentioned in Table S5. In this work, special attention was given to ensure a maximum concentration of 0.01 M in both phases whenever possible.

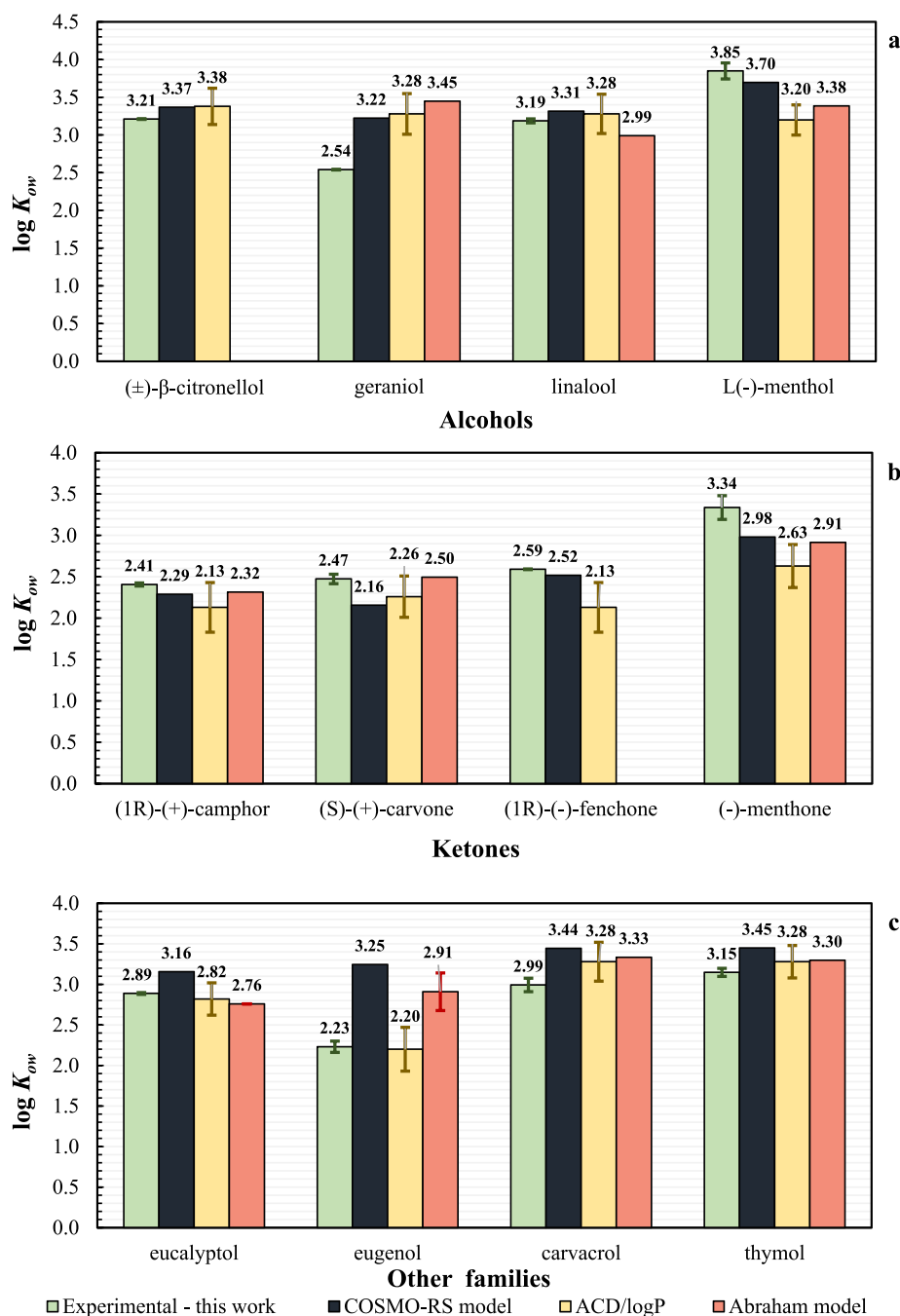
Considering the complex chemical structure of the solutes and the corresponding conformational analysis, only in some cases, a simple qualitative analysis of the experimental data can be performed. For instance, in the case of the studied monoterpene aliphatic primary alcohols (geraniol and ( $\pm$ )- $\beta$ -citronellol), the only difference in their chemical structure is that geraniol has two  $\pi$ -bonds, while  $\beta$ -citronellol has only one. The higher  $K_{ow}$  of  $\beta$ -citronellol suggests a higher interaction with 1-octanol than geraniol. Linalool is a structural isomer of geraniol, and a tertiary alcohol which may hinder its interaction with water, presenting a  $K_{ow}$  closer to that of citronellol. Moreover, the lower polarity of the cyclic saturated *L*-(-)-menthol in comparison with the other studied aliphatic alcohols manifests in its higher experimental  $K_{ow}$  value.

Among the phenolic monoterpenoids, eugenol has the lowest  $K_{ow}$ , probably due to the presence of a more polar methoxy group (hydrogen bond acceptor), absent in the isomers carvacrol and thymol. Regarding the latter, the proximity of the hydroxyl group to the isopropyl group in the case of thymol suggests that the hydroxyl group in this compound might present a weaker interaction with water compared to carvacrol, which is also observed from their experimental partition coefficients. Considering the monoterpene ketones, the experimental  $\log K_{ow}$  obtained for (-)-menthone is considerably higher. The presence of two additional  $\pi$ -bonds in (*S*)-(+)-carvone and differences in the outer surface area caused by the bicyclic rings present in (1*R*)-(+)-camphor and (1*R*)-(-)-fenchone might contribute to their lower  $K_{ow}$  compared to menthone.

**4.2. Prediction of Partition Coefficients.** The estimated partition coefficients obtained using COSMO-RS, the Abraham solvation model, and the ACD/Log *P* tool are compared with the experimental data obtained in this work in Figure 1.

All approaches present globally the same average absolute deviations (AAD), which are 0.33, 0.32, and 0.36 log units for COSMO-RS, the ACD/Log *P* method, and the Abraham solvation model, respectively. For ( $\pm$ )- $\beta$ -citronellol and (1*R*)-(-)-fenchone, the Abraham solvation model was not applied since the solute descriptors were not found in the open literature. An excellent representation of the partition coefficients of the monoterpene ketones was achieved with the COSMO-RS model (AAD = 0.22), whereas the ACS/Log *P* tool provided the best predictions for the phenolic monoterpenoids (thymol, carvacrol, and eugenol, AAD = 0.21). In the case of the monoterpene alcohols, the COSMO-RS model delivered substantially close  $\log K_{ow}$  to the experimental data obtained in this work (AAD = 0.28), being the most significant deviation observed for geraniol.

Unlike the Abraham solvation model and the ACD/Log *P* tool, which are semipredictive methods requiring a set of available experimental data to provide reliable  $\log K_{ow}$  predictions, COSMO-RS is a predictive model shown here to be capable of consistently estimating this property for most



**Figure 1.** Comparison between the experimental  $\log K_{ow}$  obtained in this work and the data estimated using COSMO-RS, the Abraham solvation model, and the ACD/Log  $P$  tool for a) ketones, b) alcohols, and c) other oxygenated families.

of the monoterpenoids addressed in this work. Furthermore, since COSMO-RS requires only the sigma profile of the solute to perform the  $\log K_{ow}$  predictions, this model can be applied to estimate the octanol–water partition coefficients of monoterpenoids. Often, additional qualitative information regarding the solvation of a solute in a liquid mixture can be obtained from those  $\sigma$ -profiles, which can be assumed as a fingerprint of the compound molecular polarity.<sup>80</sup> By analyzing the  $\sigma$ -profiles presented in Figure S1, as expected, all the monoterpenoids show the largest surface areas in the nonpolar region ( $-0.01 < \sigma < 0.01$ ), which agrees with the experimental  $\log K_{ow}$  values, between 2.2 and 3.9. Other general trends can be identified. The alcohols present similar peaks in the

hydrogen bond donor (HBD) and hydrogen bond acceptor (HBA) areas, corresponding to a single hydroxyl group. Similar profiles are obtained for the phenolic compounds with some differences. Their peaks in the nonpolar region are wider and lower, but the peaks in the HBA region are positioned at a lower screening charge density, when compared to the alcohols family. For the ketones group, the more polar surface area can be identified within the region having  $\sigma > 0.01 e/\text{\AA}^2$ , corresponding to the presence of the carbonyl group. For this family of compounds, the larger nonpolar surface of (-)-menthone stands out, consistent with its highest  $K_{ow}$ . The only ether, eucalyptol, has one of the largest surface areas in the nonpolar region, combined with a peak in the HBA region.

The quantification of the polarity differences can be further carried out by comparing the predicted partitioning of the solutes (i.e., the activity coefficients ratio). At least within each family of solutes (alcohols, phenolics, or ketones), the log  $K_{ow}$  ranking of the solutes is satisfactorily predicted by COSMO-RS. In general, the model seems to slightly overestimate log  $K_{ow}$  in the case of alcohols and phenolic compounds and underestimate them for ketones.

Finally, the ACD/Log  $P$  tool and Abraham solvation model also presented reliable predictions for many of the studied solutes, being good options for well-known and structurally simple molecules.

**4.3. Experimental Solubility Studies.** The aqueous solubilities measured in this work for (1R)-(+)-camphor, (S)-(+)-carvone, eucalyptol, (1R)-(-)-fenchone, and (-)-menthone at 298.2 and 303.2 K are presented in Table 3 along with the data obtained for the reference compounds

**Table 3. Experimental Aqueous Solubilities (in Mole Fraction) Obtained in This Work and Reported by Martins et al.<sup>38</sup> at 298.2 and 313.2 K<sup>a</sup>**

monoterpenoid	$10^5 x_{\text{terpene}}$		source
	298.2 K	313.2 K	
(1R)-(+)-camphor	13.65 ± 0.34	4.371 ± 0.086	this work
carvacrol	14.40	16.87	38
(S)-(+)-carvone	17.32 ± 0.47	16.58 ± 0.31	this work
(±)-β-citronellol	21.77	20.82	38
eucalyptol	12.75 ± 0.82	7.218 ± 0.36	this work
eugenol	22.80	25.39	38
(1R)-(-)-fenchone	23.91 ± 0.57	10.79 ± 0.19	this work
geraniol	10.27	64.29	38
linalool	13.84 ± 0.26		this work
	18.08	59.20	38
L-(-)-menthol	4.419 ± 0.095	6.198 ± 0.122	this work
(-)-menthone	2.313 ± 0.142	1.974 ± 0.114	this work
thymol	11.80	16.89	38
toluene	10.92 ± 0.35		this work
	11.27	12.03	38

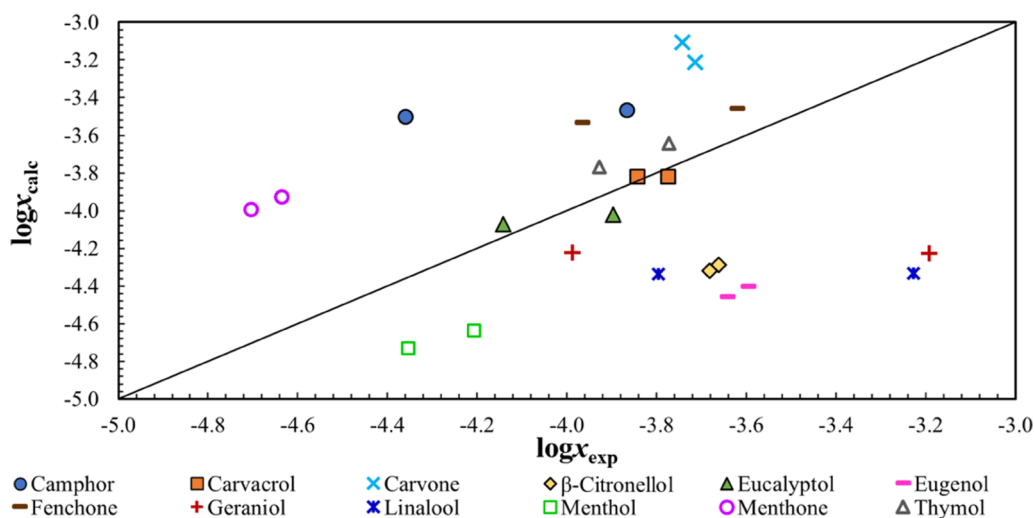
<sup>a</sup> $u(T) = 0.10$  K and  $u_i(p) = 0.05$ , respectively. Standard deviations are placed after the plus-minus sign.

(linalool and toluene) at 298.2 K. Each reported data point is an average of at least three independent samples. To provide a complete picture, the aqueous solubilities of carvacrol, (±)-β-citronellol, eugenol, geraniol, linalool, and thymol reported before<sup>38</sup> were included in Table 3. The consistency of the data obtained here is guaranteed by the low coefficients of variation, always inferior to 0.70%. Besides, the solubility data measured for linalool and toluene in this work are close to the data previously obtained by Martins et al.<sup>38</sup> using dialysis tubing cellulose membranes.

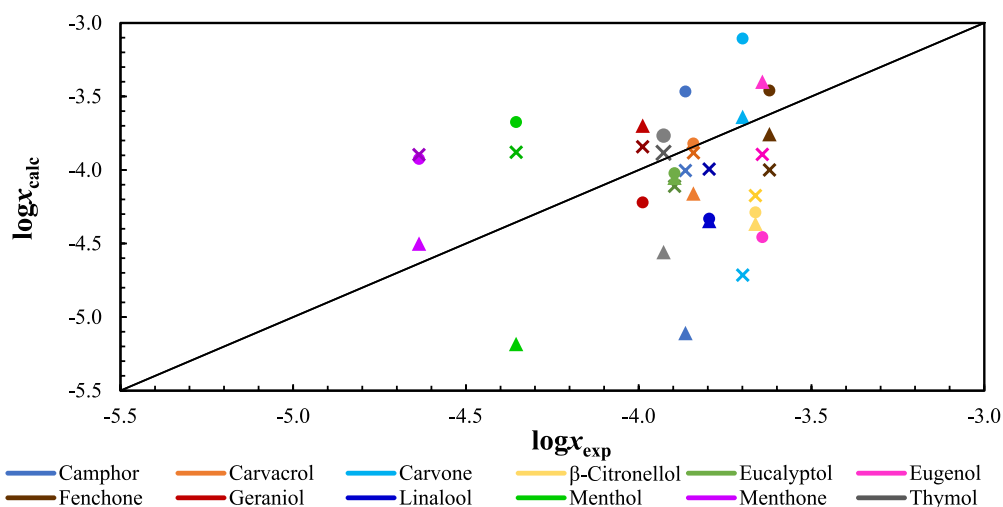
From all the solubilities measured at 298.2 K, the highest values were obtained for (1R)-(-)-fenchone ( $x = 23.9 \times 10^{-5}$ ) and eugenol ( $x = 22.8 \times 10^{-5}$ ), whereas (-)-menthone ( $x = 2.31 \times 10^{-5}$ ) and L-(-)-menthol ( $x = 4.42 \times 10^{-5}$ ) presented the lowest values. These results are generally consistent with the lipophilicity ranking derived from the partition coefficients data, as the latter two have the highest  $K_{ow}$  and eugenol the lowest. At 313.2 K, (-)-menthone is still the less soluble monoterpene ( $x = 2.0 \times 10^{-5}$ ), but geraniol registered the highest solubility in water ( $x = 64.3 \times 10^{-5}$ ). Although significant differences are observed in the absolute values data listed in Table 3, the solubilities of all the monoterpenoids fall in the ( $10^{-4}$ – $10^{-5}$ ) order of magnitude, confirming their strong hydrophobic nature already evidenced by the high log  $K_{ow}$  presented in section 4.1.

Among the phenolics, eugenol presents the highest solubilities. Since this compound has a methoxy substituent attached to the aromatic ring, it might form stronger hydrogen bond interactions with water than thymol and carvacrol. Regarding the aliphatic monoterpene alcohols, the solubility of linalool and geraniol are 3.3 times and 6.3 times higher at 313.2 K than at 298.2 K, respectively, being the compounds presenting the most significant solubility change with the temperature. The solubilities of the phenolic alcohols are about 1 order of magnitude higher than the solubilities of L-(-)-menthol in water, which can be related not only to the presence of the aromatic ring but also to the higher acidity of the hydrogen in the hydroxyl group attached to the phenyl group as in thymol.<sup>97</sup>

For eucalyptol (ether) and all the monoterpene ketones being studied, the solubilities decreased as the temperature increased, being the highest reduction observed for (1R)-



**Figure 2.** Comparison between the experimental and predicted by COSMO-RS mole fraction solubilities at 298.2 and 313.2 K.



**Figure 3.** Comparison of the predicted mole fraction solubilities at 298.2 K using the COSMO-RS model (○), the EPI Suite software (×), and the GSE approach (△).

(+)-camphor (68%) and (1R)-(-)-fenchone (55%). Although an inverse relationship between the solubility and the temperature is less common, this behavior has already been reported for eucalyptol<sup>98</sup> and some monoterpene ketones.<sup>99</sup>

A complete overview of the experimental aqueous solubility data available for the monoterpenoids covered in Table 3 is presented in Table S6 of section SM4, along with a detailed critical analysis. For camphor, carvone, fenchone, and menthone, no water solubility data was found in the open literature at 313.2, but a few studies were found for each monoterpenoid, while the description of the solubility as a function of temperature is scarce. Therefore, as will be observed in the next section, some inconsistencies are evident. Still, details such as stirring and settling time, purity, and isomeric form of the solute are not given. Nevertheless, the consistency of the results and procedure can be assured by the results obtained with the two reference molecules, toluene and linalool.

**4.4. Water Solubility Prediction.** The solubility estimates at 298.2 and 313.2 K obtained with COSMO-RS, at the BP-TZVP level of theory, are compared to the experimental results in Figure 2.

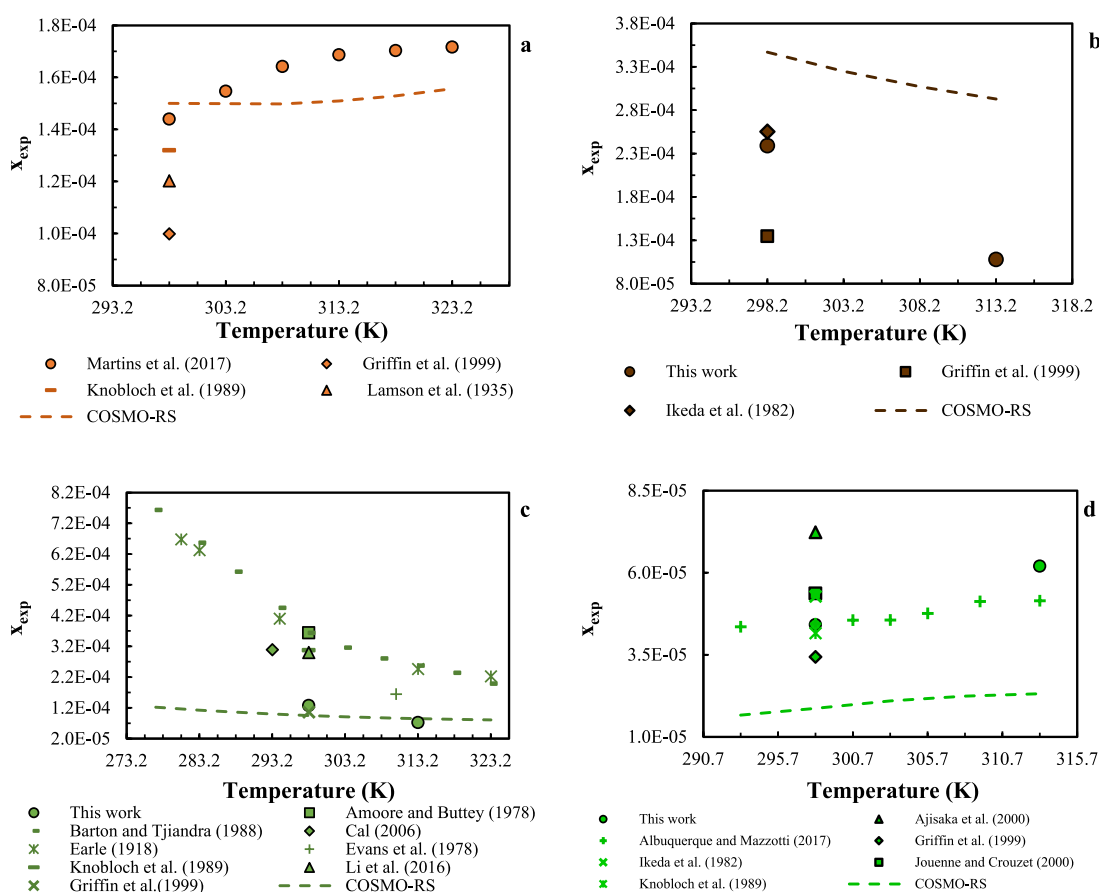
The model fairly describes the solubility in water of most terpenoids, presenting a global AAD of 0.48 in log units, which is comparable to the results obtained in other studies describing the aqueous solubility of organic solutes using COSMO-RS<sup>55,100–102</sup> and other hybrid and predictive methods.<sup>90,103–105</sup> The best predictions were obtained for carvacrol, eucalyptol, and thymol, where the absolute deviations between the experimental and predicted solubilities (at 298.2 and 313.2 K) are not higher than 0.15 log units. Higher deviations, however, are observed for alcohols, some ketones, and eugenol, particularly at 313.2 K. For ketones, COSMO-RS generally overestimates the solubility values, whereas the model delivers lower solubilities than the experimental data observed for aliphatic alcohols and eugenol. This is a consistent trend with the predictions of the partition coefficients, as the  $\log K_{ow}$  was overestimated in the case of alcohols and phenolic compounds and underestimated for ketones.

For comparison purposes, the General Solubility Equation (GSE) proposed by Yalkowsky and coauthors<sup>90</sup> and the EPI Suite WATERNT v 1.1. software<sup>106</sup> were tested to predict the solubilities in water of the selected solutes at 298.2 K. These methods are based on a direct correlation of the aqueous solubility of a nonelectrolyte solute with the octanol–water partition coefficient, being simple options for aqueous solubility screening without the need of any additional parameter. In the case of the GSE approach, the  $\log K_{ow}$ 's obtained in this work were employed along with the melting points listed in Table S2 (for the solid terpenoids at room temperature) to predict the aqueous solubilities, whereas the EPI Suite WATERINT is a pure fragmental approach.<sup>91</sup> The estimated solubilities using the GSE, EPI Suite WATERINT, and COSMO-RS are compared with the experimental data in Figure 3 and in Table S7 of section SM5 of the Supporting Information.

The EPI Suite software and the COSMO-RS thermodynamic model reasonably describe the solubilities of most of the monoterpenoids being studied at 298.2 K, achieving global AADs (in log basis) of 0.35 and 0.38, respectively. Both models offer a very good description of the solubilities of eucalyptol and phenolic monoterpenoids, except for eugenol with COSMO-RS, while the outlier solute family is the ketones (AADs of 0.57 and 0.48 for EPI Suite and COSMO-RS, respectively). The overall performance of the GSE, however, is weaker (AAD = 0.44), presenting the highest deviations for the monoterpenoids which are solid at room temperature. Although this method takes into account the melting point of solid solutes in the calculation of the solubility values,<sup>90</sup> this correction term seems to lead to considerably lower water-solubility estimations of the solid monoterpenoids than the experimental values listed in Table S6, especially for camphor and thymol, which present the highest melting points. Nevertheless, the GSE approach provided a very good description of the solubility of the ketones which are liquid at room temperature (carvone, fenchone, and menthone), with an AAD of 0.11, performing better than the other two tested models for this group of solutes.

Although the EPI Suite and the GSE approaches are simple tools capable of providing qualitative water-solubility pre-





**Figure 4.** Comparison between the predicted solubilities with the experimental data for a) carvacrol, b) fenchone, c) eucalyptol, and d) menthol.

dictions (at 298.2 K) for most of the studied terpenes, these methods are not fully predictive, which prevents their use in the full picture of the aqueous solubility phenomena. For instance, the EPI Suite WATERINT module is a fragment-based method, and the quality of the estimations is highly dependent on the employed training set, which might favor specific chemical families. Furthermore, both EPI Suite and the GSE are unable to provide solubility predictions at temperatures other than 298.2 K, which is a strong drawback in comparison with more robust tools, such as the COSMO-RS model. Attempting to develop a fully predictive approach using the GSE, the  $K_{ow}$ 's predicted by COSMO-RS were applied in the GSE, resulting in a much higher AAD, 0.61 log units. The predicted values using this approach were also included in Table S7 of the Supporting Information.

To more deeply understand the potentialities of the COSMO-RS model in describing the aqueous solubility phenomena, the model was also employed to describe the solubility-temperature curves of the selected monoterpenoids, and the results are compared with the available experimental solubility data (presented in Table S6) in Figure 4 and Figure S2 of section SMS. The solubility curves of four terpenoids from different chemical families are presented in Figure 4: carvacrol (phenol), fenchone (ketone), eucalyptol (ether), and menthol (alcohol), while the same information for the remaining monoterpenoids is included in Figure S2. For practical viewing purposes, some evident outliers were excluded from both figures.

The model generally provides water-solubility estimations in the same order of magnitude for three of the four chemical families evaluated (phenol, ketone, and ether). In fact, the model offers an excellent description of the solubility data obtained here for eucalyptol and previously reported by us<sup>38</sup> for carvacrol and thymol. For alcohols, COSMO-RS tends to underestimate the solubility values, being the highest deviations found for the linear alcohols (predicted values are 1 order of magnitude lower than the experimental data), particularly at higher temperatures. Although significant progress has been made since the COSMO-RS model has been proposed,<sup>41</sup> the well-known difficulties of the model in representing the complex hydrogen-bond interactions<sup>80</sup> still limits the description of the solubilities of systems where those interactions are relevant, such as in the case of the solubilization of alcohols in water.

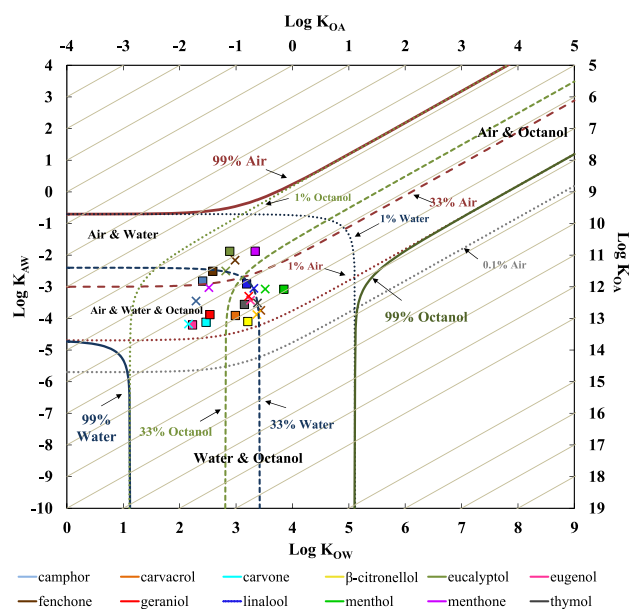
Nevertheless, COSMO-RS can describe the temperature solubility trends of most of the monoterpenoids studied in this work, including all the ketones and eucalyptol, where most of the available experimental data suggest that the solubility decreases as the temperature increases. In fact, this is a notable achievement for a predictive model, which is a great advantage in comparison with other structural-based or semiempirical approaches, often limited to perform predictions at 298.2 K.

The high inconsistency of the available aqueous solubility data for some monoterpenoids at 298.2 K, mainly for citronellol, eucalyptol, geraniol, and menthone, also deserves to be noted. In these cases, significant differences are observed among the reported data, easily spotted by the high coefficients

of variation of the available solubility data, superior to 40%. This illustrates how challenging it is to acquire reliable water-solubility data for sparingly soluble solutes, such as the monoterpenoids being studied. In this context, the use of powerful predictive tools, such as the COSMO-RS model and EPI Suite, for a fast water-solubility screening is welcome, sometimes presenting accuracies close to those found when comparing independently obtained experimental data.

**4.5. Environmental Distribution.** The model proposed by Gouin and coauthors<sup>56</sup> was used to assess the distribution of the monoterpenoids in the different environmental media (air, water, and octanol) at 298.2 K and is described in detail in section SM6 of the Supporting Information. Briefly, the octanol–water partition and the air–water partition coefficients ( $K_{aw}$ ) of the solutes are introduced in a hypothetical two-dimensional diagram representing the environmental compartments, and the probable dispersion of the solute is determined by the relationship between  $K_{ow}$  and  $K_{aw}$ . The latter is directly calculated from water solubility data along with vapor pressures, which are available in the literature.<sup>59–61,63,78,107–111</sup>

In Figure 5, the chemical space diagram for the monoterpenoids and toluene is presented. Two different



**Figure 5.** Chemical space diagram of the 12 monoterpenoids investigated in this work. The filled squares and the crosses represent the predicted distribution approaches i and ii, respectively.

approaches were tested to assess the distribution of the solutes between the environmental media: (i) experimental  $K_{ow}$  and water solubility obtained in this work along with experimental vapor pressures found in the literature and (ii) predicted  $K_{ow}$ , solubilities, and vapor pressures using COSMO-RS. The filled squares in Figure 5 represent the predicted distribution using approach i, while the crosses correspond to that obtained with approach ii. The lines (99%, 1%, and 0.1%) represent the boundaries for each environment medium, being the upper left and lower left regions rich in air and water, respectively, while the octanol-rich region is in the lower right part of the space diagram. The vapor pressures collected from the literature and

predicted using COSMO-RS are listed in Table S8 of section SM6.

In general, both approaches result in similar distribution profiles of the solutes among the different environmental media, showing once more the robustness of COSMO-RS in describing the equilibrium properties analyzed in this work. The best matches are found for carvone, citronellol, linalool, and thymol, while the higher inconsistencies are observed for geraniol, eugenol, and menthone. In fact, both methodologies suggest that all the monoterpenoids are probably partitioned between the three compartments, often persisting in fractions above 33% in the water medium.

From all the investigated monoterpenoids, eucalyptol is the most persistent in the air compartment, which is due to its higher vapor pressure at 298.2 K (229.53 Pa)<sup>60</sup> along with moderate solubility in water (1.09 g·L<sup>-1</sup>) and the octanol–water partition coefficient (2.89). On the other hand, menthol is mainly partitioned in the organic media, which is expected considering its high  $K_{ow}$  (3.85) and low aqueous solubility (0.38 g·L<sup>-1</sup>) and vapor pressure (5.04 Pa).<sup>78</sup> Besides, the phenolic monoterpenoids (thymol, carvacrol, and eugenol) are predominantly distributed between the water and the organic compartments.

## 5. CONCLUSIONS

In this work, the octanol–water partition coefficients of a set of 12 structurally different monoterpenoids (ketones, alcohols, phenolic alcohols, and ethers) were measured using the analytical shake-flask method combined with GC/UV–vis analysis. Besides, new aqueous solubility data were obtained for six of the previously mentioned set of solutes at 298.2 K and at 313.2 K. Since the water solubility of the other six monoterpenoids has already been reported by us in a previous study,<sup>38</sup> a complete analysis of the aqueous solubility phenomena for the whole set of monoterpenoids is presented. Whenever possible, the partition coefficients and solubilities determined in this work were critically compared with the data available in the open literature. A good agreement was found between most of the data obtained in this work and the average literature values, although, in some cases, the extent of the comparisons is restricted due to high inconsistencies between the data found in the literature. To the best of our knowledge, the solubilities of camphor, carvone, fenchone, and menthone in water at 313.2 K are reported here for the first time.

Despite its full predictive character, COSMO-RS showed very satisfactory results in the prediction of the partition coefficients (global AAD of 0.33 log units) and aqueous solubilities (AAD = 0.38, at 298.2 K), where globally the EPI Suite WATERINT was the best (AAD = 0.35) for aqueous solubility, and the ACD/Log P tool provided the best description of the partition coefficients (AAD = 0.32).

Lastly, the distribution of the monoterpenoids in the different environmental media is predicted by introducing the retrieved physicochemical equilibrium properties into a chemical space diagram. The distribution of monoterpenoids into the three environmental compartments, water, air, and organic matter in the soil and sediments, has been proposed based on the experimental data, and a very satisfactory consistency has been found with that applying COSMO-RS. The prediction of the presence of other important representatives of the terpene family, such as monoterpenes and sesquiterpenes, in the environment calls for new efforts on the investigation of fundamental physicochemical properties of

these compounds as well as for a critical assessment of the available data, often scarce and inconsistent.

## ■ ASSOCIATED CONTENT

### SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.iecr.1c04196>.

Analytical method for quantification of experimental partition coefficients and solubilities; list of maximum wavelengths used to build UV–vis calibration curves;  $\sigma$ -profiles for solutes, octanol, and water obtained using COSMO-RS; summary of melting properties used in modeling step for solid monoterpenoids; list of Abraham solvation model descriptions for solutes and octanol–water system; detailed comparison of experimental partition coefficient and aqueous solubility data obtained in this work and available in the literature; summary of predicted solubility values using COSMO-RS model, GSE method, and EPI SUITE software; description of methodology employed to assess environmental distribution of monoterpenoids; and summary of predicted and experimental vapor pressures used in environmental distribution analysis (PDF)

## ■ AUTHOR INFORMATION

### Corresponding Authors

**Simão P. Pinho** – Centro de Investigação de Montanha (CIMO), Instituto Politécnico de Bragança, 5300-253 Bragança, Portugal; [orcid.org/0000-0002-9211-857X](https://orcid.org/0000-0002-9211-857X); Phone: +351 273303086; Email: [spinho@ipb.pt](mailto:spinho@ipb.pt); Fax: +351 273313051

**Olga Ferreira** – Centro de Investigação de Montanha (CIMO), Instituto Politécnico de Bragança, 5300-253 Bragança, Portugal; [orcid.org/0000-0001-8414-3479](https://orcid.org/0000-0001-8414-3479); Phone: +351 273303087; Email: [oferreira@ipb.pt](mailto:oferreira@ipb.pt); Fax: +351 273313051

### Authors

**Sérgio M. Vilas-Boas** – Centro de Investigação de Montanha (CIMO), Instituto Politécnico de Bragança, 5300-253 Bragança, Portugal; CICECO – Aveiro Institute of Materials, Department of Chemistry, University of Aveiro, 3810-193 Aveiro, Portugal; School of Chemical Engineering (FEQ), University of Campinas (UNICAMP), 13083-852 Campinas, Brazil; [orcid.org/0000-0001-8179-935X](https://orcid.org/0000-0001-8179-935X)

**Mariana C. da Costa** – School of Chemical Engineering (FEQ), University of Campinas (UNICAMP), 13083-852 Campinas, Brazil

**João A. P. Coutinho** – CICECO – Aveiro Institute of Materials, Department of Chemistry, University of Aveiro, 3810-193 Aveiro, Portugal; [orcid.org/0000-0002-3841-743X](https://orcid.org/0000-0002-3841-743X)

Complete contact information is available at: <https://pubs.acs.org/doi/10.1021/acs.iecr.1c04196>

### Notes

The authors declare no competing financial interest.

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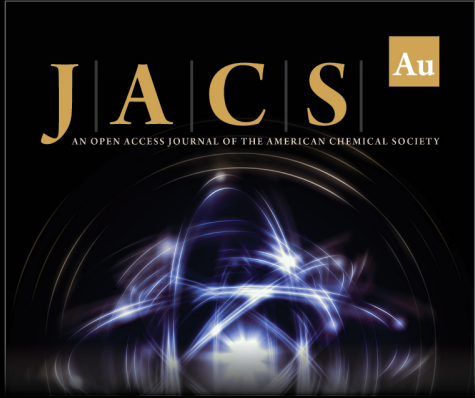
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