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Studies on the Solubility and Partition of Terpenes in Aqueous Organic Solvents

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Abstract

Terpenes are organic compounds, produced by various plants, in particular conifers, and which represent the main constituents of the essential oils of these plants. The vast majority of terpenes are widely used in different industrial sectors such as flavors, perfumes, spices, cosmetics or food additives, and due to their biological activity they are also used for pharmaceutical and medical purposes.

It is therefore very crucial to carry out studies on the solubility or the partition coefficient of a terpene, since these equilibrium data make it possible to optimally determine the adequate solvent for the extraction or purification of a certain compound while by limiting costs, losses and environmental nuisances. In this context, this work reports the solubility and the partition coefficient of four terpenes (thymol, eugenol, carvacrol and camphor) in organic and aqueous solvents (ethanol/water, l octanol/water, methanol/heptane, ethyl acetate /water, ethanol) at 298.15 and 313.15 K, using the shake-flask method and Abraham's solvation model to describe solubility data.

The results obtained were satisfactory with regard to the solubility of thymol in ethanol (at 298.15 K and 313.15 K) or the partition coefficient of eugenol in the octanol/water solvent mixture (at 298.15 K), since they are in agreement with the experimental data available in the literature. On the other hand, for carvacrol and camphor, no solubility study was found in the literature for the temperatures studied. However, the conclusive results obtained could reassure on the effectiveness of the methods used in this work.

Resumo

Os terpenos são compostos orgânicos, produzidos por várias plantas, em particular coníferas, e que representam os principais constituintes dos óleos essenciais destas plantas. A grande maioria dos terpenos são amplamente utilizados em diferentes setores industriais como aromatizantes, perfumes, especiarias, cosméticos ou aditivos alimentares, e devido à sua atividade biológica também são utilizados para fins farmacêuticos e médicos.

Portanto, é muito importante realizar estudos sobre a solubilidade ou o coeficiente de partição de um terpeno, pois esses dados de equilíbrio permitem determinar de maneira ótima o solvente adequado para a extração ou purificação de um determinado composto, limitando custos, perdas e impactos ambientais. incômodos. Neste contexto, este trabalho relata a solubilidade e o coeficiente de partição de quatro terpenos (timol, eugenol, carvacrol e cânfora) em solventes orgânicos e aquosos (etanol/água, l octanol/água, metanol/heptano, acetato de etila/água, etanol) a 298,15 e 313,15 K, usando o método do frasco agitado e o modelo de solvatação de Abraham para descrever os dados de solubilidade.

Os resultados obtidos são satisfatórios quanto à solubilidade do timol em etanol (a 298,15 K e 313,15 K) ou ao coeficiente de partição do eugenol na mistura solvente octanol/água (a 298,15 K), pois estão de acordo com os dados experimentais disponíveis. na literatura. Por outro lado, para carvacrol e cânfora, nenhum estudo de solubilidade foi encontrado na literatura para as temperaturas estudadas. No entanto, os resultados conclusivos obtidos podem reafirmar a eficácia dos métodos utilizados neste trabalho.

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Chapter I. State of Art

I.1 Introduction

I.1.1 Importance and Objectives

Terpenes are the main constituent of essential oils of certain plants and certain flowers or fruits, such as lemon and orange. For example eugenol is the main constituent of clove oil, thymol is the main constituent of thyme essential oil, while camphor is the main constituent of camphor essential oil, etc. Terpenes, and their oxygenated derivatives, terpenoids, belong to what is arguably the largest and most diverse class of natural compounds. As components of essential oils, most of them are widely used in different industrial sectors such as flavorings, perfumes, spices, cosmetics or food additives, and due to their biological activity, used for pharmaceutical and medical purposes. In the pharmaceutical field, for example, they are used as excipients for improving skin penetration of the active principles of medicaments.

It is important to determine the physicochemical properties of terpenes, in order to establish their compatibility with other compounds. Among these properties, solubility is a fundamental physical property involved in the implementation of separation processes (such as extraction, precipitation or crystallization in the food, pharmaceutical and cosmetic industries), and purification (such as refining, etc.). In this sense studies have been carried out on the liquid-liquid (LLE) or solid-liquid (SLE) equilibria of binary mixtures of terpenes, water, and organic solvents.

The primary objective of this work is therefore the determination of the solubility and the partition coefficient of terpenes in organic solvents (methanol, ethanol, 1-propanol, butanone, ethyl acetate, etc.) and aqueous (water), followed by the application of thermodynamics models such as Abraham solvation model.

I.1.2 Contents

This work aims to determine the solubility and the partition coefficient of terpenes in organic and aqueous solvents. For this reason, we have subdivided this as follows:

- In the first part the description of the different compounds highlighted in this work is given, and concepts such as solubility and the partition coefficient defined.
- The second part will present the analytical methods used as well as experimental work and obtained data.
- Finally, the presentation of the conclusions and future work.

I.2 Literature Background

I.2.1 Compounds (thymol, camphor, eugenol, carvacrol)

I.2.1.1 Thymol

Thymol is a phenol found in thyme oil and in the essential (volatile) oils of several other plants. It occurs as colorless crystals with a characteristic aromatic odor. It is soluble in alcohols, fat and oil and sparingly soluble in water. It is used in particular for its antiseptic, antibacterial and antifungal properties as well as for stabilizing pharmaceutical preparations.

Its chemical formula is $C_{10}H_{14}O$, with a molar mass of 150.2176 ± 0.0093 g/mol (with C 79.96%, H 9.39%, O 10.65%). Its physical properties are: melting point of 49 to 51 °C, boiling point 233 °C, water solubility of 1.4 g/dm^3, and density of 0.97–0.93 g/cm^3. **Figure 1** shows the chemical structure of thymol. [1]

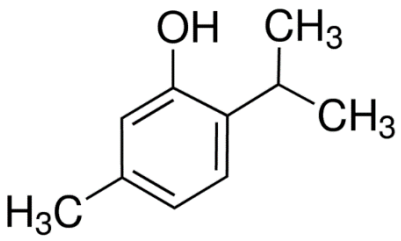

Figure 1. Chemical structure of thymol.

I.2.1.2 Camphor

Camphor (**Figure 2**) is a solid bicyclic organic compound derived from camphor tree, appearing as a crystalline solid, white, translucent, smooth to the touch, scratched by the nail, with a lively odor, bitter and aromatic flavor. It is a ketone of formula $C_{10}H_{16}O$, with a molar mass of 152.233 4 ± 0,009 4 g/mol (with C 78.9 %, H 10,59 %, O 10.51 %), and from which camphene is synthesized. Almost insoluble in water, it is soluble in organic solvents, glycerin, and very soluble in ether, benzene, acetic acid, oils and essences. Nitric acid converts it into camphoric acid $C_{10}H_{16}O_4$. Its specific gravity is 0.992 at 10 °C. It melts at 179.75 °C and boils at 204 °C. [2]

Camphor is used in the production of celluloid (the case of the brothers John and Isaiah Hyatt), explosives, as well as in medicine for its antiseptic and slightly anesthetic properties (it constitutes for example the main component of tiger balm). In 1831–32, it was used to control the cholera morbus epidemic and then against the Asian flu in 1957–1958. However, camphor is a poison when ingested in large amounts and it can also be an anaphrodisiac. [3]

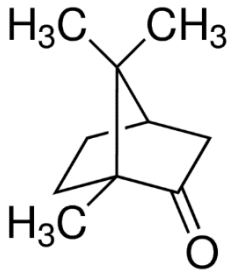

Figure 2. Chemical structure of camphor.

I.2.1.3 Eugenol

Eugenol is an aromatic compound of the phenylpropene family, with the molecular formula $C_{10}H_{12}O_2$, with a molar mass of 164.201 1 ± 0,009 4 g/mol (C 73.15 %, H 7.37 %, O 19.49). It has a melting point (at 1 bar) of −9 °C, boiling point of 253 °C, and a density of 1.06 g/cm^3 at 20 °C. It is poorly soluble in water and insoluble in salt water. However, it is very soluble in ethanol and dichloromethane, and somewhat in chloroform.

In its natural state, eugenol is a phenol that forms most of the essence of cloves, but also that of allspice or clove cinnamon; it is also found in the leaves of the bay laurel (Umbellularia californica). **Table 1** below represents the percentage of eugenol in some essential oils. [4]

Table 1. Mass percentage of eugenol in essential oils from different sources. [4]

Plant	Concentration in essential oil
Eugenia caryophyllata	70–90%
Cinnamomum cassia L.	70–90%
Cinnamomum zeylanicum	70–90%
Dianthus caryophyllus L.	30%
Ocimum basilicum L.	30–80%
Ocimum gratissimum L.	50–90%
Ocimum sanctum L.	70%
Ocimum suave	80%
Pimenta acris	40–60%
Pimenta officinalis	65–90%

In the pharmaceutical field, it is used for its antiseptic and analgesic properties. It is also found in many drugs, especially in mouthwashes to treat infections, but it is also found in an ointment to facilitate breathing in lung diseases. It is also used for the synthesis of vanillin, the main constituent of natural vanilla. **Figure 3** represents the structure of eugenol.

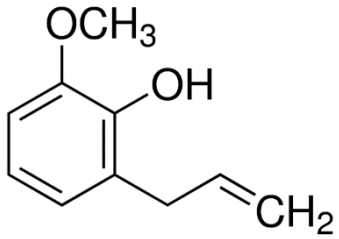

Figure 3. Chemical structure of eugenol.

I.2.1.4 Carvacrol

Carvacrol is found in essential oils obtained in particular from oregano, thyme, or monarda. In thyme, the essential oil contains, depending on the subspecies, from 5% to 75% of carvacrol, while the subspecies of savory (Satureja) contain from 1% to 45% (mass percentages).

Its chemical formula is $C_{10}H_{14}O$, with a molar mass of 150.2176 ± 0.0093 g/mol (with C 79.96%, H 9.39%, O 10.65%). It boils at a temperature of 236.85 °C and has a melting point of 2.5 °C, and a density of (20 °C) 0.9772–0.98 g/cm^3.

It can be synthesize by fusing cymol-sulfonic acid with caustic potash; by the action of nitrous acid on 1-methyl-2-amino-4-propyl benzene; or by heating carvacrol with glacial phosphoric acid or by dehydrogenating carvone with a catalyst. It can also be extracted from oil of oregano by the action of a 50% potassium hydroxide solution. It is a thick oil which is set at 20 °C in a mass of crystals whose melting point is at 0 °C, and the boiling point at 236-237 °C.

Figure 4 above shows the structure of carvacrol.

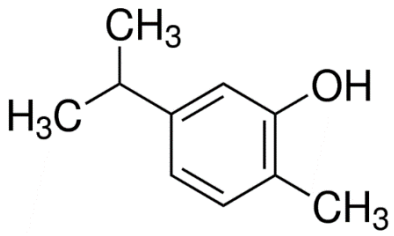

Figure 4. Chemical structure of carvacrol.

I.2.2 Solubility and Partition Measurements

I.2.2.1 Solubility

Solubility can be defined as the ability of a substance, called a solute, to dissolve in another substance, called a solvent, to form a homogeneous mixture called a solution. Solubilization refers to this process of dissolution.

A solvent is a substance, in the liquid or supercritical state at the temperature of use, which has the property of dissolving, diluting or extracting other substances without chemically modifying them and without modifying itself. Solvents are used in very diverse sectors such as degreasing, paints, inks, detergents, organic synthesis. Water is the most common solvent, the solution then being referred to as an aqueous solution. Organic compounds in them tend to dissolve well in solvents that have properties similar to themselves. This is because polar molecules generally dissolve well in polar solvents and nonpolar molecules generally dissolve in nonpolar solvents. Solvents can be classified according to several aspects: the chemical nature of the compound, the polarity, the physicochemical properties, the sector of use, the toxicity, the origin (petroleum or agro-based), etc.

Several studies have therefore been carried out in order to determine the solubility of certain terpenes in aqueous and organic solvents and among these studies, namely the study on the solubility of terpenes in water and their environmental distribution that appeared in the Journal of Molecular Liquids in a work developed within the research group at IPB. The experimental data from these studies are reported in **Table 2**. [6]

Table 2. Experimental mole fraction (xterpene) of terpenes in water as a function of temperature and at atmospheric pressure (Martins et al., 2017).

	$x_{terpene}$ (10^4)					
	298.15 K	303.15 K	308.15 K	313.15 K	318.15 K	323.15 K
Geraniol	1.027(0.330)	1.390(0.066)	3.747(0.366)	6.429(0.099)	9.222(0.315)	12.652(0.087)
Linalool	1.808(1.756)	3.320(0.406)	4.723(0.236)	5.920(0.424)	8.438(0.849)	11.080(1.306)
DL-Citronellol	2.177(0.114)	1.874(0.391)	1.866(0.327)	2.082(0.028)	2.487(0.068)	3.084(0.044)
Thymol	1.180(0.060)	1.327(0.047)	1.457(0.069)	1.689(0.150)	1.890(0.050)	–
Eugenol	2.280(0.083)	2.305(0.522)	2.538(0.275)	2.539(0.150)	2.856(0.932)	3.118(0.920)
Carvacrol	1.440(0.173)	1.547(0.073)	1.642(0.098)	1.687(0.163)	1.703(0.090)	1.717(0.054)
p-Cymene	0.048(0.002)	0.069(0.003)	0.099(0.005)	0.124(0.004)	0.151(0.016)	0.189(0.007)

The expanded uncertainty for a 95% confidence interval is presented between brackets. The standard uncertainty of temperature is u(T) = 0.1 K.

From the data collected we find that, with the exception of DL-citronellol, the solubility of terpenes in water increases monotonically with temperature. In addition, the solubilities of the molar fractions are of the order of 10^{-4} confirming the "hydrophobic" character to which this class of compounds is generally attached and showing that the dissolved terpenes can be considered at infinite dilution. Compound structures such as the terpene, p-cymene, an alkylbenzene, present at 298.15 K, the lowest solubilities while the eugenol terpenoid, a phenylpropene, present the highest, which could be explained by the presence of oxygen groups.

I.3 Experimental Work

In the beginning of this project it was important to make a bibliographical study on the experimental methods to measure the solubility of solids and liquids in organic and aqueous solvents. In addition, knowing a database already available on the work of other researchers, of different terpenes, will allow us to have a benchmark for comparison with the results we will obtain.

I.3.1 Experimental Methods

Several procedures can be used in studying the solubility of solids in a liquid, such as the thermodynamic and kinetic solubility methods.

Under certain conditions, it is not possible to perform the thermodynamic solubility determination method, due to the large sample requirement, low throughput and laborious sample preparation. At this stage therefore, we can use the kinetic solubility determination methods as an alternative. [7, 8]

I.3.1.1 Determination of thermodynamic solubility

There are several methods for measuring the solubility of solids in liquids. They are generally classified into two main groups, namely: analytical and synthetic methods. The analytical method, also called the shake flask method, is the possibility of measuring a large number of samples simultaneously, but it remains tedious and time-consuming all the same.

- **The shake flask method**

Proposed by Higuchi and Connors (1965), this method is considered the most reliable and is also the most widely used measurement method for measuring the solubility of several compounds. In fact, this method involves adding an excess amount of solute to the solvent, so that a saturated solution can be formed, and the solubility is measured under isothermal-isobaric conditions (Hefter & Tomkins 2003; Baka and Takács-Novák, 2008). In this method, we prepare a sample under saturated conditions, which is thermostatically controlled and kept under stirring until the system equilibrium and this can oscillate from 12 hours to days, depending on several parameters such as: the equilibrium method applied (Apley et al. 2015), the nature of the solute and the solvent, the agitation employed and the amount of material used. Once equilibrium is reached, the excess solute is removed from the stock solution by simple filtration. To determine therefore the solubility of the stock solution, various analytical methods can be used, notably such as UV-Vis spectrophotometric analysis which is generally considered to be the most common and the simplest analytical method, then we have the HPLC methods (which could detect any impurities or degradation products if a highly selective method were used), we also have X-ray diffraction (XRD) (Hefter & Tomkins 2003; Mota et al. 2010), and differential scanning calorimetry (DSC) to analyse the residual solid separated from the saturated solution confirming possible transformations of the solid phase during equilibration.

❖ **Synthetic method**

This method (Ren et al., 2005), also called laser monitoring technique, is based on the disappearance of the solute from the solution mother (mixture of solvent and solute) monitored by a laser beam. The history of this method dates back to 1886 and was first introduced by Alexejew and then modified by other research groups. In order to completely dissolve the solute, we can either perform a temperature modification or add a known amount of the solvent. According to Ren et al. (2005) this synthetic method would be much faster and more reliable than the analytical method.

Figure 4 illustrates a schematic representation of the most complete configuration used in the synthetic method. [9]

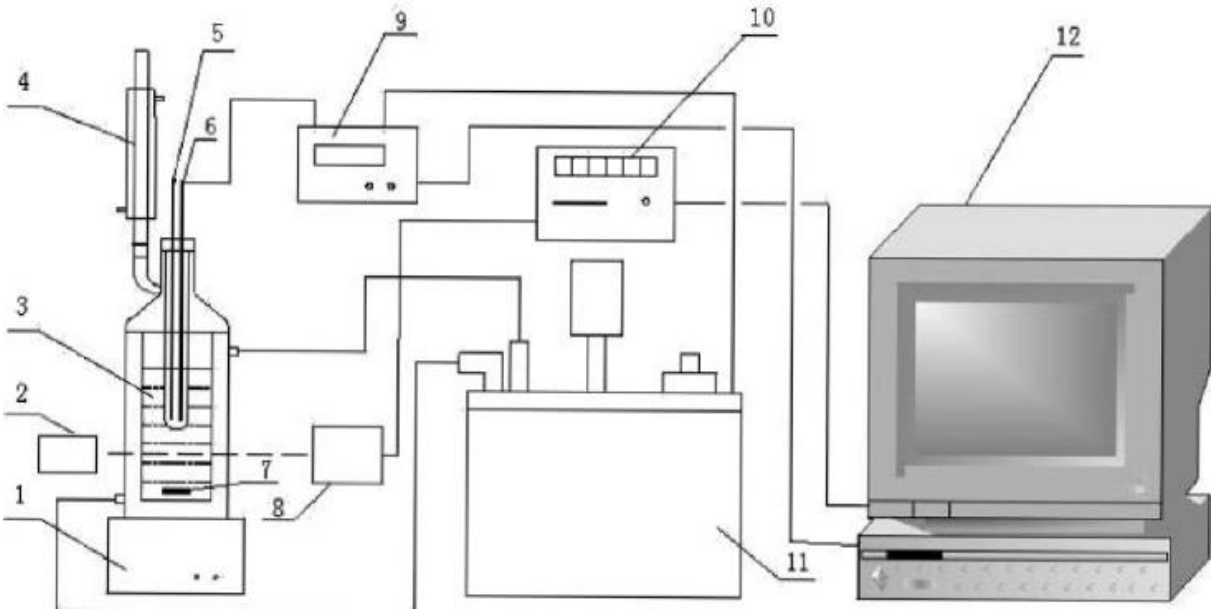

Figure 5. Schematic representation of the synthetic method for the determination of the solubility of solid solute.

The different compoenets are as follows: 1, magnetic stirrer 2, laser generator; 3, jacketed glass container; 4, condense the pipe; 5, thermometer; 6, thermocouple; 7, rotor; 8, photoelectric transducer; 9, controller; 10, laser force display; 11, constant temperature bath; 12, workstation.

I.3.1.2 Determination of kinetic solubility

The advantage of this method over methods for determining thermodynamic solubility is its ability to be easily automated, its precision, speed and the fact that it requires less amount of solute (Pan et al., 2001; Alsenz and Kansy, 2007; Hoelke et al. 2009). Moreover, it has drawbacks such as the non-evaluation of the crystalline effect on the solubility, the consoling action of dimethyl sulfoxide (DMSO) and its applicability is good for compounds which have a solubility greater than 10^{-6} molar. In order therefore to determine the solubility of a solute solvent mixture, the following methods are used: nephelometric, UV spectroscopic and HPLC methods which are discussed in the following. [10]

❖ **UV-Vis spectroscopic method**

In order to determine the kinetic solubility, there are two methods using UV-VIS spectroscopy: the first method is based on turbidimetry and the other is based on the intensity of the light absorbance as a function of the concentration (Pan et al., 2001).

- **UV-Vis spectroscopic method 1**

In this method, sample preparation is done by taking a concentration of 10 milimoles of a solute, which will be dissolved in appropriate amounts in DMSO. Then this stock solution is used to prepare sample solutions in the range of $5*10^{-7}$ to $5*10^{-4}$ mole fraction. For concentrations greater than 10^{-4} molar, solutions prepared by direct dilution of the stock solution and for lower concentrations serial dilutions are used when the diluent is a buffer. These dilutions are carried out directly in a 96-well plate with the total concentration of 5% of DMSO and the final volume of ≈200 µL (Pan et al., 2001; Hoelke et al. 2009). This optimal volume is based on the fact that the light scattering (for a specific condition) is almost constant for a range of particle sizes which make the process reproducible and precise. This method provides a wider range of wavelengths to choose from for reading sample turbidity (190-1000 nm) (Pan et al., 2001). The lower the wavelength, more particles are detected. However, in practice wavelengths greater than 500 nm are used. This is because most organic compounds that have UV absorbance (for example, contain a benzene ring) also have a fluorescence property and can interfere with turbidimetry which reads the amount of reflected light (or sunlight). fluorescence emission). An example of this is phenol red which has light absorption at 430 and 560 nm and is output at these wavelengths, resulting in fluorescence emission (Pan et al., 2001). Another limitation is the UV absorbance of most plastic plates (Pan et al., 2001). [10]

- **UV-Vis spectroscopic method 2**

In this method, a dilution of the sample in a range of $7*10^{-9}$ to $5*10^{-4}$ molar is performed. But after precipitation of the stock solution by the aqueous solution, the samples are filtered on another plate. In this part, 20% acetonitrile is added to the filtered samples to prevent precipitation of solute during analysis. Then the plate is read with a 96-well UV-Vis spectroscopy machine and the recorded data is changed to molar concentration (determined by the calibration curve obtained by standard solutions using another plate) (Pan et al. , 2001; Hoelke et al. 2009). [10]

- **HPLC method**

Commonly referred to as high performance liquid chromatography, HPLC is an efficient analytical technique that can be combined with a saturated solution generation column to measure aqueous solubilities. Sample preparation for this method is the same as for the UV-Vis 2 spectroscopic method and sample transfer to the 96-well plate is not required. However, sample filtration is performed before injection into the HPLC or in-line filtration is applied. A calibration curve is necessary for the determination of the concentrations of the prepared samples. This method is the most accurate compared to other mentioned methods (detection limit $<10^{-8}$ molar), it can also reduce colloidal dispersions, adsorption of solute in the walls of the material, minimize sample loss by evaporation and the use of organic solvents (Mota et al. 2010). But we must consider that it consumes much more time (about 6 hours for 96 samples) (Pan et al., 2001; Hoelke et al. 2009). A comparison between this method and the UV-Vis spectroscopic method is given in **Table 3. [10]**

Table 3. Comparison between kinetic solubility determination methods.

Method	Calibration	Specificity	Easy	Cut off	Speed
UV/Vis 1	Not required	Low	Yes	<500 nm	High
UV/Vis 2	Required	Medium	No	<250 nm	Medium
HPLC	Required	High	No	No	Low

Baka et al. (2008) recommend certain precautions to be taken when handling the solutions to be studied, in order to reduce the error that could occur when performing the shake-flask method. These precautions include: taking measurements at a standard and controlled temperature, having a quantity of excess solid in the solution which varies in the order of 1 to 2 mg/ml of solution in order to avoid sampling problems, check the equilibrium time for each compound studied (however, a minimum time of about 24 hours to reach, in addition to 6 hours of agitation and 18 hours for sedimentation).

I.4 Thermodynamic Modeling

The thermodynamic modeling that we will use in this study is Abraham's solvation model (Abraham, 1998. 2010, 2013). Indeed, it is widely used to predict for example the partition coefficients for conventional organic and ionic liquid, for the partition of drug molecules between blood and some organs of the body, for partitioning into micelles and for the prediction of solvation enthalpies in organic solvents and ionic organic fluids. This solvation model is based on two linear free energy relations (LFER), as clearly enumerated by Abraham and colleagues. One of these relationships is to measure the solute partition between two condensed phases (illustrate by equation 1). [11]

$$Log\ (Ps) = c + eE + sS + Aa + bB + vV \qquad (1)$$

Where log (*Ps*) is the solvent/water partition coefficient. Under reasonable conditions, this model can also be used to predict the solubility of organic compounds in organic solvents as follows.

$$\boldsymbol{log\ Ss = log\ Sw + c + e\ E + s\ S + a\ A + b\ B + v\ V} \quad (2)$$

where Ss is the molar concentration of the solute in the organic solvent, Sw is the molar concentration of the solute in water, (*c, e, s, a, b*) are the coefficients of the solvent, and (*E, S, A, B, V*) are the descriptors of the solute: *E* is the excess molar refractivity of the solute in units of (cm^3/mol), *S* is the dipolarity/polarizability of the solute, *A* and *B* are the acidity and basicity global or summative of the hydrogen bond, and *V* is the characteristic McGowan volume in units of (cm^3/mol).

For solubility calculations, only the first LFER quantifying the transfer of solute between the organic solvent and water was considered in this work. In this case, the separation between water and a solvent (*PS*) is defined as the ratio between the molar solubilities in organic solvent (*Ss*) and in water (*Sw*) as follows:

$$\boldsymbol{Ps} = \frac{Ss}{Sw} \quad \textbf{(3)}$$

According to Abraham et al. [11], certain constraints apply to the application of equation 3. These constraints are:

- equality between the solid phase in equilibrium with water and the organic solvent
- the activity coefficient of the secondary medium of the solute in the two phases is close to unity; the same chemical species (undissociated, if ionizable) must be present in each phase.

To date, solvent coefficients have been determined for over 90 common solvents, and group contribution methods have been developed to approximate all coefficients for certain classes of solvents that do not have been published yet. The solvent coefficients in the support material relate to dry solvents or solvents which absorb very little water (hexane, toluene, etc.). Studies have extended the applicability of the Abraham model by developing open models, using open descriptors from the Chemistry Development Kit (CDK) which can be used to predict Abraham's solvent coefficients of any organic solvent, directly from the structure.

In order to directly compare different solvents, Abraham and coworkers found it advantageous to first recalculate the solvent coefficients with the coefficient *c* equal to zero. For this they used equation (1) to calculate the values of the log P for 2144 compounds from the Open Data database of compounds with known Abraham descriptors, and this allowed to have the following equation

$$\mathbf{log\ P = e0\ E + s0\ S + a0\ A + b0\ B + vv\ V} \qquad \mathbf{(4)}$$

In the above equation, the index zero indicates that $c = 0$ was used in the regression and in order to treat all solvents equally. **Table 4** lists the original solvent coefficients as well as the adjusted coefficients $c = 0$. Comparing the coefficients, one observes that the coefficients systematically move in the same way. That is, solvents with negative *c* values all saw an increase in *e* and *b* (and a decrease in *s*, *a* and *v*) on recalculation, while solvents with positive *c* values all saw an increase in *s*, *a* and *v* (and a decrease in *e* and *b*).

Table 4. Solvent coefficients in the Abraham Solvation model.

c	e	s	a	b	v	Solvent	e 0	s 0	a 0	b 0	v 0
0.351	0.223	−0.150	−1.035	−4.527	3.972	methyl acetate	0.195	−0.068	−0.924	−4.571	4.152
0.328	0.369	−0.446	−0.700	−4.904	4.150	ethyl acetate	0.343	−0.369	−0.597	−4.945	4.319
0.248	0.356	−0.501	−0.867	−4.973	4.281	butyl acetate	0.336	−0.443	−0.788	−5.005	4.409
0.276	0.334	−0.714	0.243	−3.320	3.549	methanol	0.312	−0.649	0.330	−3.355	3.691
0.222	0.471	−1.035	0.326	−3.596	3.857	ethanol	0.453	−0.983	0.396	−3.623	3.971
0.243	0.213	−0.575	0.262	−3.450	3.545	ethanol/water(90:10)vol	0.193	−0.518	0.339	−3.481	3.670
0.172	0.175	−0.465	0.260	−3.212	3.323	ethanol/water(80:20)vol	0.161	−0.424	0.314	−3.233	3.411
0.063	0.085	−0.368	0.311	−2.936	3.102	ethanol/water(70:30)vol	0.079	−0.353	0.331	−2.944	3.134
−0.040	0.138	−0.335	0.293	−2.675	2.812	ethanol/water(60:40)vol	0.141	−0.344	0.281	−2.670	2.792
−0.142	0.124	−0.252	0.251	−2.275	2.415	ethanol/water(50:50)vol	0.135	−0.285	0.207	−2.257	2.342
−0.221	0.131	−0.159	0.171	−1.809	1.918	ethanol/water(40:60)vol	0.148	−0.211	0.103	−1.782	1.805
−0.269	0.107	−0.098	0.133	−1.316	1.414	ethanol/water(30:70)vol	0.128	−0.161	0.049	−1.283	1.276
−0.252	0.043	−0.040	0.096	−0.832	0.916	ethanol/water(20:80)vol	0.063	−0.099	0.017	−0.801	0.787

Chapter II. Experimental Studies

II.1 Presentation

It is important to study the solubility of organic compounds, in order to determine the best solvent with which they could interact. Indeed, each solvent, whether organic or aqueous, does not interact in the same way when it is mixed with other substances and this can be explained by the fact that these solvents have or not the same properties than the substances to which they are mixed.

The study of solubility therefore makes it possible to establish the compatibility between one or more liquid-liquid or solid-liquid mixtures, and therefore to determine the most suitable solvent for the extraction of a given substance.

II.2 Material and experimental method

II.2.1 Experimental method

II.2.1.1 Chemicals

The compounds were used as received, without any further processing. Ultrapure water was obtained at the LQA laboratory (at the IPB) by a reverse osmosis process using a Direct-Q ® water purification system. All the information relating to the nature of these compounds is listed in Table 5.

Table 5. Molar mass (MM), dosage (purity wt.), supplier, CAS and normal boiling points (NBP) of each of the components used in this work.

Component	MM (g/mol)	Mass Purity	Supplier	CAS	NBP (ºC)
Thymol	150.22	≥ 0.995	Sigma	89-83-8	49.6
Eugenol	164.20	0.99	Aldrich	97-53-0	253.2
Camphor	152.23	0.99		76-22-2	209
Cavacrol	150.22	0.99	SAFC	499-75-2	2.5

II.2.1.2 The shaken flask method

In order to carry out the study on the solubility of the terpenes, for each compound, Erlenmeyer flasks were use to prepare the saturated solutions presenting a reasonable quantities of solute in excess and between 12 to 24 ml of solvent. A magnetic bar is used for stirring. Then, each cell was covered with allure paper to avoid any solvent evaporation and reduce the impact or alteration of the different elements of the solution by light. After the equilibrium cell were placed on a plate shaker inside a thermostatic bath (Lauda Instruments, model E20, Ecoline 025) operating with distilled water and regulated at a temperature of approximately 37 °C. This can be seen in the Figure 6.

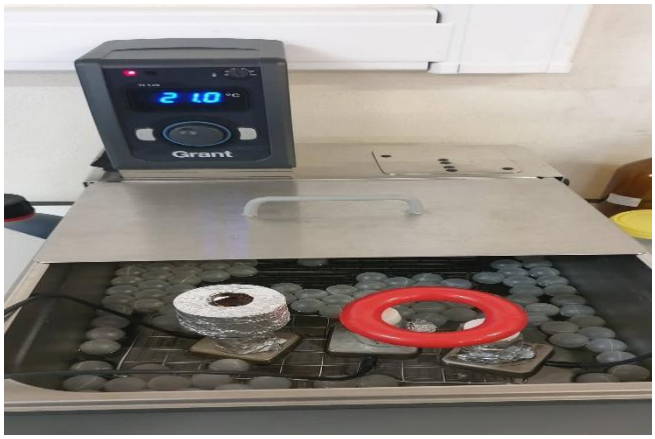

Figure 6. Thermostatic bath.

Based on previous studies that have been conducted to determine the required stirring and settling times for similar systems (Mota et al. 2009; Mota et al. 2012), an average time of agitation and settling of 24 hours and 8 hours were selected, respectively. It must be ensured beforehand that there will be an excess of solutes at the end of the process. For this, fast tests before putting our solutions in the thermostatic bath for agitation and decantation were carried out. These tests consisted of previously preparing a stock solution with an adequate amount of solute, which are placed on a magnetic stirrer for stirring, then after a few minutes the solution is observed to see if have any solute (solid) is perceptible. Depending on this, the solute is added or not, little by little, until the observation with the naked eye of its presence in the solution.

It is only after this step the solution is placed in the thermostatic bath to follow the the process. This step previously described is necessary because it makes possible to ensure that more easily the system reaches the equilibrium over time and also to minimize the experimental errors. This is all the even more important if the solubility of solutes in water is much lower than the solubility in organic solvents (according to available data from the literature).

Then, once decanted, three samples of volume varying between 1.5 and 5 ml of the stock solution are taken, using plastic syringes with metal needles, then placed in previously weighed glass bottles. Then, a dilution is carried out with the solvent (the volume of which depends on the amount of solute taken) and the vial containing the saturated solution plus the solvent is weighed. After that, a UV-VIS analysis is performed to determine the absorbance and with the help of a calibration curve, the solubility is determined. Figure 7 shows the equipment needed for sampling.

Figure 7. Syringes and filters used to collect the samples from the solutions.

II.2.1.3 Partition coefficient

The chosen methodology used to determine the partition coefficient was based on those of the traditional shake flask method. [12; 13]. In effect, for each compound to be studied, about 0.18 ml of solute and 24 ml of solvent mixture were used, after transferred to a previously weighed Erlenmeyer flask, this being the mother solution. Then three graduated tubes of 14 ml each were weighted, into which we introduce 7 ml of the mother solution and 7 ml of heptane. The mixture was weighed again. The tubes were then manually inverted for 5 min at room temperature to facilitate the distribution of the solute in the two phases, then continuously mixed

in an Eppendorf ThermoMixer C at 298.2 ± 0.5 K with continuous shaking (300 rpm) for about 6 h. The system was allowed to settle overnight (approximately 16 hours) then placed in a centrifuge (rpm = 1500, T = 25 °C) for approximately 40 minutes, followed by a decantation period of at least 1 hour in the Thermomix before sampling.

For each phase of the saturated solution, two samples are taken using polypropylene syringes which are placed in previously weighed bottles (12 in total) and then the whole is weighed. Then, a well-defined quantity of ethanol is introduced into each bottle and weighed again. One then proceeds to a manual agitation to mix and then one proceeds to the UV analysis of each solution, in order to determine the absorbance of each sampled phase. The results of the absorbance of each phase will therefore allow to calculate the partition coefficient of the terpene under study.

II.2.2 The materials used

To carry out our study, we used several materials such as; a balance, a thermomixer, a centrifuge, and a UV measuring device.

- A weighing scale

Graduated between 1 mg and 101 g and brand KERN (ABT 100-5M, e= 1mg, d=0.01 mg) it allowed us to carry out all the necessary weighings. These weighings concerned both the glassware used to contain the solutions and the solutions. Figure 8 shows the balance used in this work.

Figure 8. A scale graduated from 1 mg to 101 g.

❖ Thermomixer

It is an eppendorf brand device (T=25°C, 7750 ppm, 15 mL) which allows the different mixtures to be mixed while maintaining excellent temperature control to guarantee complete, reliable and reproducible test results. Figure 9 shows the device used in this work.

Figure 9. Thermomixer from Eppendorf.

❖ A centrifuge

It is a device that separates the compounds of a mixture according to their difference in density by subjecting them to centrifugal force while maintaining a constant temperature. The mixture to be separated can consist either of two liquid phases, or of solid particles in suspension in a fluid.

❖ A UV-VIS measuring device

This is a very important device (UV/VIS Spectrometer T70) used during the work. Thanks to this device it is possible to measure the absorbance of each compound and thus determine their concentration in different solutions.

Figure 10 shows the device used.

Figure 10. A UV-VIS measuring device.

II.3 Solubility Modeling

II.3.1 Abraham Solvation Model

The thermodynamic model used in this study is the Abraham solvation model (Abraham, 1998. 2010, 2013). Indeed, it is widely used to estimate the partition coefficients for conventional organic and ionic liquid solvents. This solvation model is based on two linear free energy relations (LFER), as clearly enumerated by Abraham and co-workers. One of these relations consists in measuring the distribution of the solute between two condensed phases (illustrated by equation 1 below). [14; 15]

In order to determine the partition coefficients studied in this work with the Abraham solvation model, the descriptors solute and the solvent were extracted from the literature [18, 19] and are presented in the Tables 6 and 7.

Table 6. Abraham model parameters collected from literature for the monoterpenoids under study.

Monoterpenoid	***E***	***S***	***A***	***B***	***V***	**Reference**
(1R)-(+)-camphor	0.579	0.850	0.000	0.642	1.316	[22]
carvacrol	0.824	0.810	0.560	0.430	1.339	[23]
eugenol	0.943	0.787	0.427	0.550	1.354	[22]
thymol	0.822	0.840	0.440	0.430	1.339	[23]

Table 7. Descriptors of the Abraham model collected from literature for octanol-water system. [20-21]

Solvent	c	e	s	a	b	v	Reference
Octanol/Water	0.088	0.562	-1.054	0.034	-3.46	3.814	25

Chapter III. Results and Discussion

III.1 Presentation

In the previous chapters the materials and methods used in this work were presented and the different compounds we used were also described. In this chapter, the work carried out in the laboratories of the CIMO IPB (Chemical Engineering Department) is presented, as well as the results and discussions. This work will focus on the study of the solubility of terpenes (thymol, eugenol, camphor and carvacrol) in aqueous and organic solvents, as well as the comparison of the results obtained with the results of similar studies rcarried out by other researchers.

III.2 Solubility and partition coefficient in water and organic solvents

III.2.1 Solubilityof Camphor

III.2.1.1 Calibration Curve

In this study to determine the solubility of an organic compound a calibration curve was needed. This is a relation generated by experimental means, relating the concentration of the solution (on the x-axis) to the observable variable (the absorbance of the solution) on the y-axis. The curve is therefore obtained by measuring the concentration and the absorbance of several prepared solutions, called calibration standards. Once the curve is drawn, the concentration of the unknown solution can be determined by placing it on the curve as a function of its absorbance or some other observable variable.

Figure 11 and Table 8 below represents the data collected and the calibration curve of camphor in ethanol/water (50%/50%) that we established to determine its solubility in water and in the water/ethanol solvent mixture in different proportions.

Table 8. Data to the calibration curve of camphor.

Calibration curve			
Sample ID	Concentration (g/ g de soluion)	Absorbance	Média UV
A	0.00487338	1.069 1.071	1.070
B	0.00338678	0.731 0.728	0.7295
D	0.00076922	0.154 0.154	0.154
E	0.0012354	0.258 0.256	0.257
F	0.0015189	0.325 0.324	0.3245
G	0.002004241	0.433 0.431	0.432
H	0.002274337	0.489 0.492	0.4905

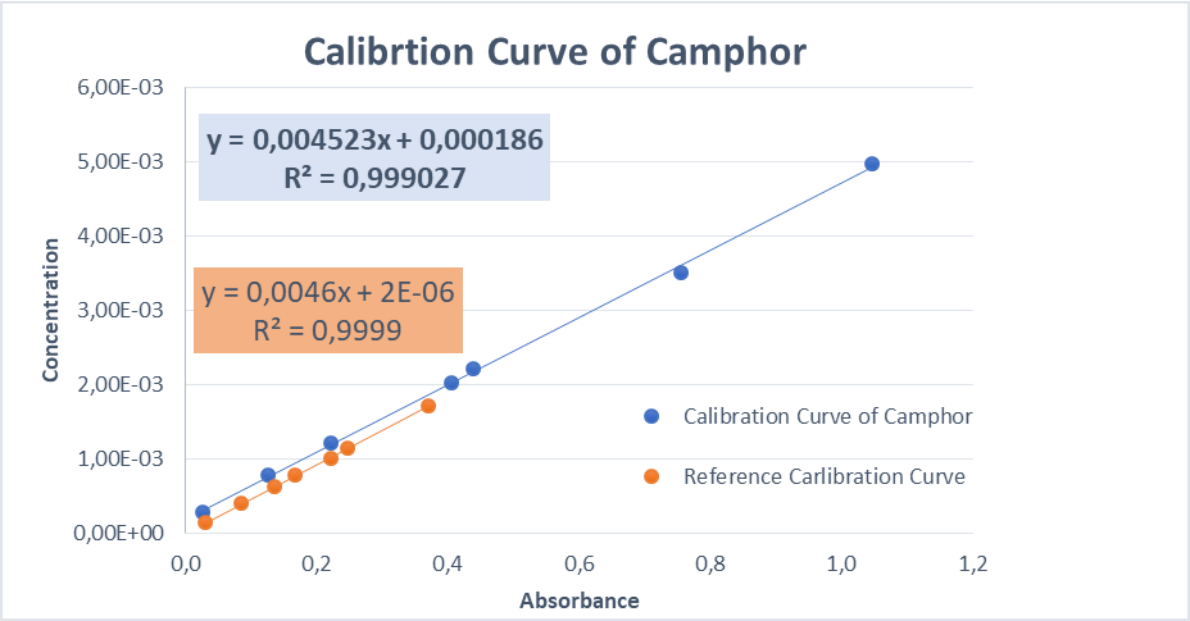

Figure 11. Calibration curve of

III.2.1.2 Solubility of camphor in ethanol/water

In this work, several experiments to determine the solubility of camphor were carried out. Indeed, solubility experiments were performed in pure water, pure ethanol and then in a solvent mixture containing water and ethanol at different mass percentages. This mixture of solvents is prepared beforehand before being mixed with the solute (camphor) whose solubility it is desired to know. Figure 12 and the Table 9 below represent the results obtained.

Table 9. Solubility data of camphor at 298.15 K.

%Ethanol	Solubility (g solute / g solution)
0	0,0018
10	0,0029
20	0,0059
30	0,0159
40	0,0539
50	0,1497
70	0,4183
90	3,0396
100	7,0831

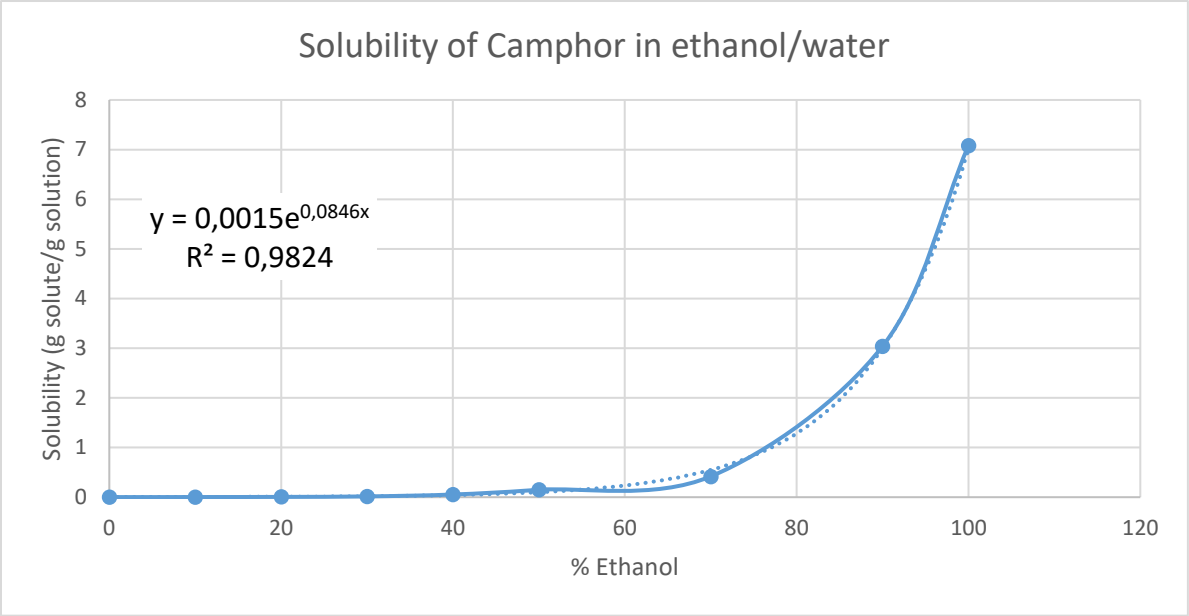

Figure 12. Solubility of camphor in water/ethanol at 298.15 K.

From the previous curve, we see that the higher the percentage of ethanol in the solvent (the ethanol/water mixture), the higher the solubility of camphor, that increases in an exponencial form, what is common in cosolvency. The solubility of camphor in water is very small.

III.2.2 Solubility of thymol

III.2.2.1 Calibration Curve

The table 12 and figure 14 below represent the data collected and the calibration curve of thymol in ethanol/water (50%/50%) that we established to determine its solubility in the predefined solvents.

Table 10. The data collected for the calibration curve of thymol.

Sample ID	Concentration (g/ g de solution)	Absorbance	Absorvance Average
A	$1.325*10^{-5}$	0.155 0.156 0	0.1555
B	$2.843*10^{-5}$	0.35 0.356 0.356	0.354
C	$4.593*10^{-5}$	0.593 0.59 0	0.5915
D	$6.139*10^{-5}$	0.781 0.778 0	0.7795
E	$1.038*10^{-4}$	1.342 1.342 1.345	1.343
F	$1.2335*10^{-4}$	1.566 1.563 0	1.5645

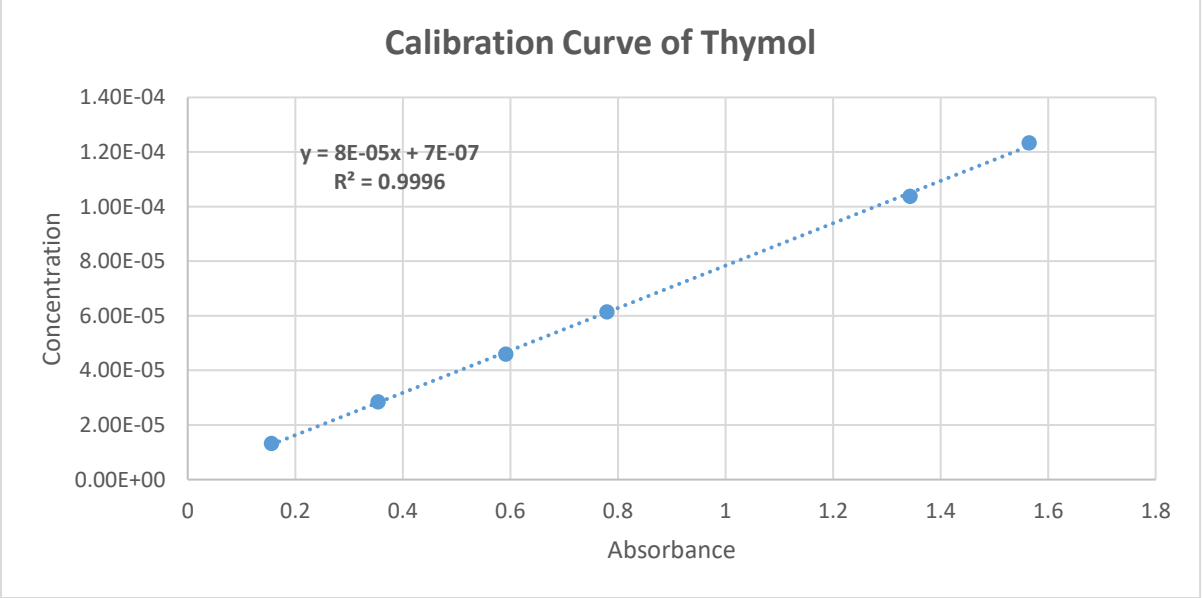

Figure 13. The calibration curve of thymol.

III.2.2.2 Solubility of thymol in ethanol at different temperatures

In this work, experiments to determine the solubility of thymol were conducted. Indeed, we carried out solubility in ethanol at different temperatures. Figure 16 shows the results obtained. The results will be discussed im section III.3.2.

III.2.3 Partition coefficient of eugenol

III.2.3.1 Partition coefficient of eugenol in different solvents

The partition coefficient experiments were conducted in several solvents such as: octanol + water, 1-butanol + water, ethyl acetate + water, methanol + heptane. This mixture of solvent is prepared before being mixed with the solute (eugenol) for which we wish to know the partition coefficient. Table 11 below presents the results obtained.

Table 11. Summary of the partition coefficients of eugenol in ARIZONA N and other biphasic systems

System	P	Standard deviation	Coefficient of Variation (%)	ARD(%) of the material balance	log(P)	Quantification method
Octanol + Water	170.31	4.07E+00	2.39%	0.98%	2.23	UV-VIS
1-butanol + water	755.75	2.11E+01	2.80%	7.11%	288	UV-VIS
Ethyl acetate + water	8101.59	4.32E+02	5.33%	8.96%	3.91	UV-VIS
Methanol + heptane	0.15	1.67E-03	113%	9.31%	-0.83	UV-VIS

As shown in the previous table, eugenol has a much higher partition coefficient in some solvent mixtures than in others. Indeed, in a mixture of solvents containing methanol + heptane, eugenol has a very low partition coefficient of the order of -0.83 compared to a mixture of solvents such as ethyl acetate+water where its partition coefficient is very high, around 3.91.

This information allows us to conclude that the ethyl acetate/water solvent mixture could be effective in extracting eugenol.

III.2.4 Partition coefficient of thymol and carvacrol in octanol-water in the literature

Several studies have been conducted to determine the partition coefficient of thymol and carvacrol in the octanol-water solvent mixture. These studies were carried out using several methods such as the RP-HPLC method, shake-flask, etc. Table 13 presents a set of data present in the literature for the octanol-water partition coefficient of thymol and carvacrol obtained from several analytical methods at 298.15 K.

Table 12. Experimental log (P) values at 298.15 K available in literature for of the studied monoterpenoids and toluene (reference compound) along with the implemented experimental procedure and reference.

Monoterpenoid	Log (P)	methodology	reference
thymol	3.57	shake-flask	Turina & al. (2006)
	3.21	shake-flask	Reiner & al. (2009)
	3.30 ± 0,01	shake-flask	Hansch & al. (1967)
	3.31 ± 0.002	shake-flask	Zhang & al. (2009)
carvacrol	3.49 ± 0.09	RP-HPLC	Griffin & al. (1999)
	3.75 ± 0.01	shake-flask	Griffin & al. (1999)
	3.14	shake-flask	Reiner & al. (2009)
toluene	2.21 ± 0.02	shake-flask	Banerjee & al. (1980)
	2.61± 0.03	shake-flask	Tayar & al. (1984)
	2.65	shake-flask	Miller & al. (1982)
	2.65	RP-HPLC	Tewari & al. (1982)
	2.69	RP-HPLC	Chin & al. (1986)

From the data collected in the table above, we find that the partition coefficient varies between 2.21 (toluene) and 3.75 (carvacrol). Very small differences are also observed between

the different values of the partition coefficient of the compounds studied, i.e. approximately 0.36 for thymol (between the highest value of the partition coefficient and the lowest value), approximately 0.35 for carvacrol and about 0.48 for toluene.

❖ Analysis of partition coefficients

The partition coefficients of thymol and carvacrol obtained by several investigators in the same system using different methods were compared to determine the mean absolute deviations (AAD). Figure 15 shows this comparison.

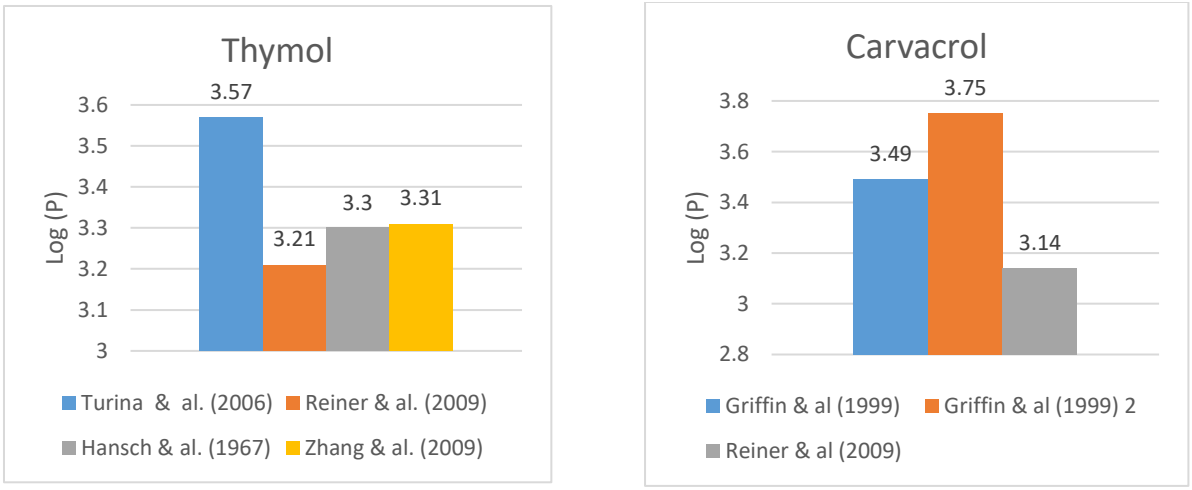

Figure 14. Comparison between the log (P) of the different analyzes of terpenes in octanol/water in the literature obtained by RP-HPLC and shake-flask methods.

The mean absolute deviations (AAD) of the log (P) of thymol and carvacrol are respectively 0.11 and 0.21, which is rather conclusive as to the reliability of the method used to determine octanol/water the partition coefficient of terpenes.

III.3 Comparison to literature data

III.3.1 Partition coefficient of eugenol in octanol/water

Several data on the partition coefficient of eugenol in the literature were found. These data allowed us to make a comparison with the values obtained in this work and the result can be seen in the Table 14.

Table 13. Experimental values of the log (P) obtained in this work and of the log (P) available in the literature for the monoterpenoids studied at 298.15 K as well as the experimental procedure implemented and the reference.

Log (P)	Methodology	Reference
2,23	shake-flask	This work
2.31	NMd	Sahu & al. (2020) [14]
2.30	shake-flask	Reiner & al. (2009) [17]
2.27	shake-flask	Tchimene & al. (2013) [20]

From the data collected log (P) value varies between 2.31 (Sahu et al. 2020) and 2.23 (this work), a difference of 0.08, showing the good quality of the results from this work. **Figure 16** shows that comparison.

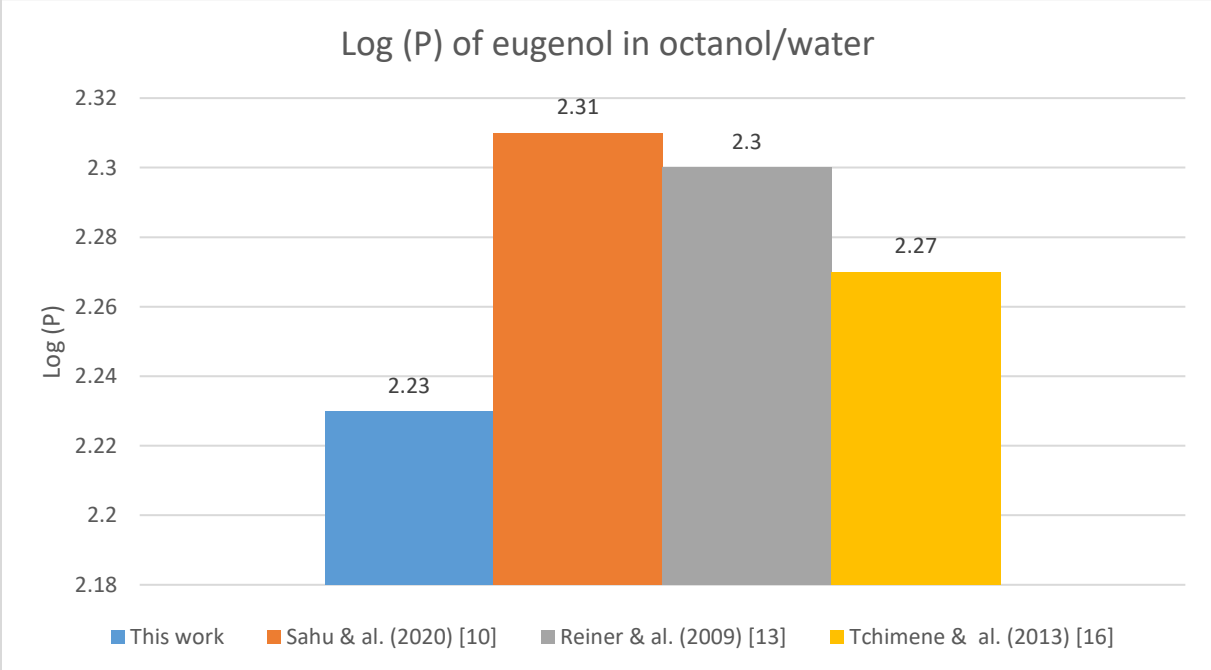

Figure 15. Comparaison between the log (P) obtained in this work and the data available in the literature.

III.3.2 Solubility of thymol in ethanol

Now a comparison between the solubility data found in this work with those available in the literature is shown. Table 15 and Figure 17 report that analysis.

Table 14. Solubility of thymol in ethanol at different temperatures.

T/K	*g solute/g solution*	*Reference*
279.15	$7.222*10^{-1}$	*Chen et al. (2016)*
283.15	$7.525*10^{-1}$	
288.25	$7.781*10^{-1}$	
293.15	$8.103*10^{-1}$	
298.15	$8.557*10^{-1}$	
303.15	$8.830*10^{-1}$	
308.15	$9.135*10^{-1}$	
313.15	$9.506*10^{-1}$	
298.15	$8.629*10^{-1}$	*This work*
313.15	$9.462*10^{-1}$	

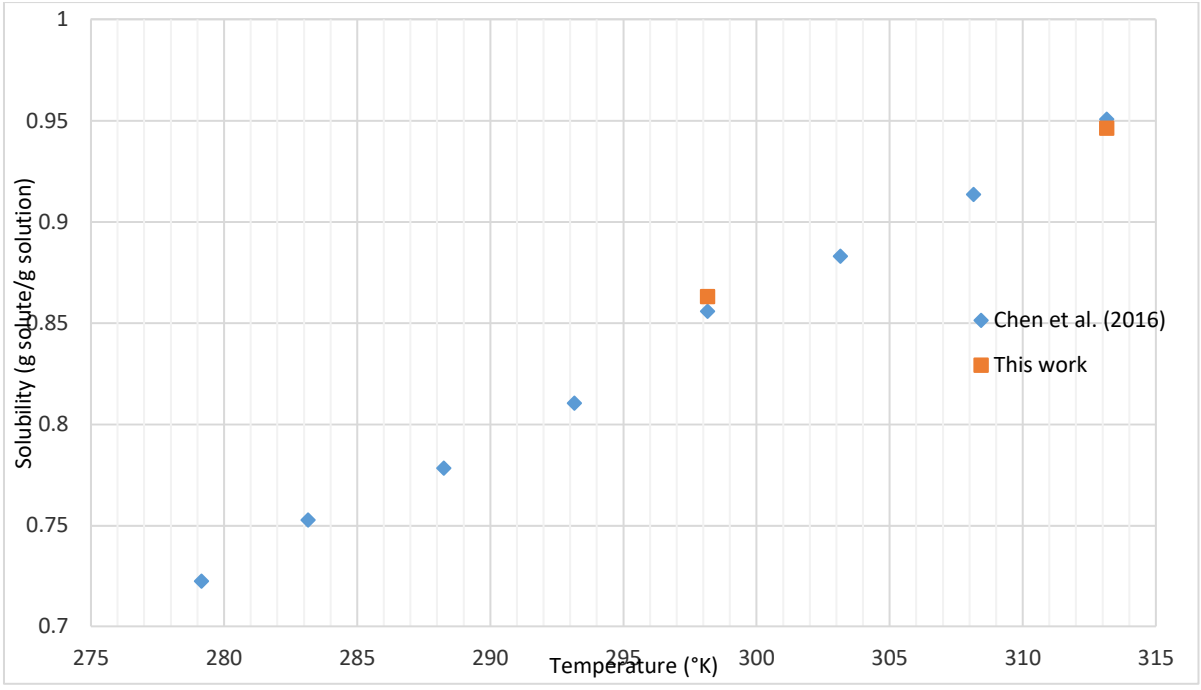

Figure 16. Comparison of the solubility of thymol in ethanol at different temperatures; this work and the data available in the literature.

From the results the solubility of thymol in ethanol solubility increases with temperature. Moreover, according to the results one observes that, at similar temperatures, one has practically the same values of solubility, that is to say 0.8629 (mass fraction) for this work and 0.8556 for the experiment carried out by Chem. et al. (2016)-JCT at 298.15K; or 0.9462 for this work and 0.9506 for the experiment conducted by Chem et al. (2016)-JCT at 313.15 K. This therefore informs us about the effectiveness of the methodology used in this work to determine the solubility of thymol in ethanol.

Chapter IV. Conclusions and Future Work

The study of the solubility and the partition coefficient of terpenes in different solvents is an important step in various separation processes, such as liquid-liquid or solid-liquid extraction, since it allows us to determine the solvent more suitable for extracting any compound in the best efficiency.

Indeed, it was therefore a question in this work of determining the solubility and the partition coefficient of compounds such as thymol, eugenol, camphor and carvacrol in different mixtures of solvents (ethanol/water, octanol/water, 1-butanol/water, ethyl acetate/water, methanol/heptane), at 298.15 K and 313.15 K. To achieve this, the shake methods flask to was applied.

In view of the results obtained in this work coupled with those available in the literature, with regard to the solubility of camphor in an ethanol/water solvent mixture, the higher the percentage of ethanol in the solvent mixture, the higher the solubility. With regard to eugenol, we observed that its partition coefficient is higher in the solvent mixture ethyl acetate/water (3.9 at 298.15K) than in the other solvent mixtures (octanol/water, 1-butanol/water, methanol/heptane). Finally, an increase in solubility with temperature was observed for thymol solubility in ethanol and very similar solubility values compared to the literature.

However, although the methods to determine the solubility and the partition coefficient of terpenes were very successful given the comparison of the results obtained in this work with those available in the literature, it would be wise to broaden the research on the solubility of these terpenes in other pure and mixed solvents, in order to better assess the most appropriate solvents to dissolve them. It would be also fundamental to include some other terpenes and apply effectively modeling approaches as a preliminary solvent screening.

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