STUDIES FOR THE DEVELOPMENT OF NEW SEPARATION PROCESSES WITH TERPENES AND THEIR ENVIRONMENTAL DISTRIBUTION

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Extended Abstract

1. Summary

Terpenes belong to what is probably the largest and most diverse class of natural products with applications in several industries due to their flavor, and fragrance features. Their high number, variety of structures and chemical complexity, make of them a class of compounds for which many different and important studies are to be carried out, and questions to be answered both concerning their thermophysical properties and phase equilibria, and their impact in the extraction and purification processes as well as on their environmental impact. Both are relevant for technological developments in the biorefinery era, where these compounds may play an important role given their ubiquity, economic value and variety of applications. This thesis is related to terpenes extraction from natural sources and their subsequent separation and purification. Besides to the development of new experimental procedures for thermodynamic properties and equilibrium measurements, some theoretical approaches were also applied to this end. To create new applications for terpenes, and taking advantage of their very low solubility in water as shown by new and accurate experimental determinations, terpenes are used to prepare sustainable and cheap hydrophobic solvents within the deep eutectic solvents framework. After, based on the activity coefficients at infinite dilution measurements and COSMO-RS predictions a selection of ILs was made with potential for terpenes fractionation. Yet, and aiming at the development of new separation processes of terpenes, deep eutectic solvents composed of ammonium salts and monocarboxylic acids were also formulated and characterized. Finally, and targeting the development of accurate models for the fate of terpenes in the environment, a range of essential physicochemical properties of terpenes were measured and modelled.

2. Problem Addressed

With more than 55000 structures and a large range of applications in several industries, terpenes are a very important research topic. However, due to the high number of structures and their complexity, there are still a lot of knowledge to be gathered and questions to be answered. This thesis aims at contributing to deepen the understanding of terpenes concerning their applications; their extraction, production or deterpenation; and the environmental problems associated with natural and anthropogenic emissions. To a better understanding of this work, a schematic representation is presented in Figure 1.

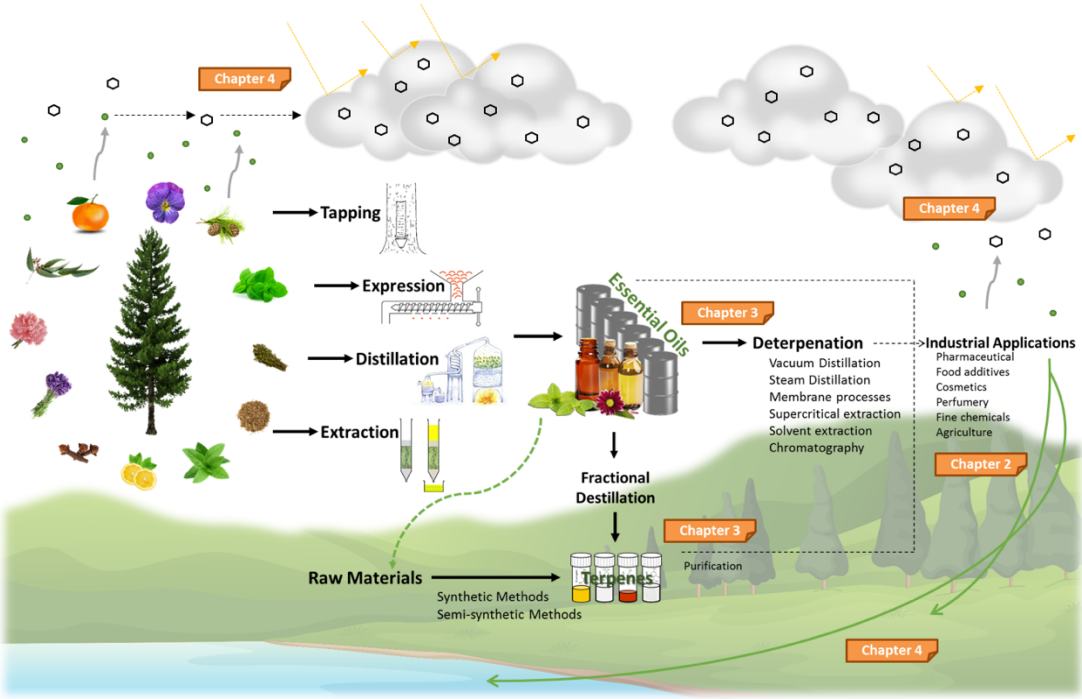

Figure 1. Schematic illustration of the work developed on this thesis.

Taking advantage of their very low solubility in water, terpenes arise as suitable candidates to prepare sustainable hydrophobic solvents to be used in novel processes and products. To the best of our knowledge, so far, only a few works reported hydrophobic eutectic mixtures and, among them, those that are liquid at room temperature are very limited. Moreover, the absence of phase diagrams is common, despite the important information they can provide on the range of compositions and temperatures for operating these systems. Chapter 2 deals with eutectic solvents and deep eutectic solvents composed by terpenes and monocarboxylic acids, and mixtures of terpenes. Phase diagrams are characterized and analyzed in the whole composition range, and physicochemical properties of the eutectic point explored.

To be used in industrial applications, terpenes must first be extracted from their natural sources, most often as essential oils. In the fractionation of these essential oils for the production of pure terpenes or their deterpenation, noxious organic solvents are commonly used. In order to replace them and to develop more efficient processes, this work investigates the use of neoteric solvents: ionic liquids and deep eutectic solvents. Chapter 3 addresses the ability of ILs to act as entrainers in separation processes and the selection of ILs as separation agents of terpenes and terpenoids – both using measurements of activity coefficients at infinite dilution and, for terpenes, the design of better ionic liquids based on COSMO-RS predictions. Based on the results of this work, the design of novel DES, composed of ammonium salts and monocarboxylic acids, are carried out and the DES solid-liquid phase diagrams characterized and modeled with PC-SAFT. Moreover, being choline chloride the most used salt used to prepare DES and since the compound decomposes upon melting, its melting properties are indirectly estimated from solid-liquid equilibria data. New eutectic systems formed by choline chloride and a fatty alcohol, or a fatty acid are then prepared and characterized.

Many plants release scented vapors formed mainly by monoterpenes. Labeled recently as volatile organic compounds, these turn into aerosols once in the atmosphere. Moreover, the emerging applications of terpenes are leading to the increase of their anthropogenic production and thus, their fate in the air, soil and aquatic compartments is concerning the environmentalists. Thus, in Chapter 4, a range of essential physicochemical properties of terpenes are accurately measured and modelled or calculated, contributing for the development of accurate models for the fate of terpenes in the environment, and to develop predictive theoretical models for these properties. When deriving the activity coefficients at infinite dilution, the lack of physical properties was noted, namely the critical properties – essential to many thermodynamic models. Accordingly, the first work presented in this chapter responds to this using group-contribution methods and equations of state for the estimation of critical properties of terpenes, and the best set is recommended. In another context, since ILs have been studied to extract and fractionate terpenes, their environmental fate, especially in water, is also important. Thus, the mutual solubilities, densities and viscosities for a range of ILs and water are measured and discussed and the same experimental method is then applied to measure the solubility of terpenes in water. However, it proved to be inappropriate due to the formation of emulsions after stirring which cause sampling problems. A new technique is then developed and firstly applied to sparingly soluble N-(diethylaminothiocarbonyl)benzimido derivatives providing accurate results and thus applied to determining the solubility of terpenes in water. Moreover, the measured properties, along with some others from literature, are used

to draw a two-dimensional plot describing a hypothetical chemical space that allows a first screening of compounds with respect to their probable distribution in the environment once released.

3. State of the Art

At a time when new chemical products are increasingly sought after to address societal needs without neglecting the growing focus on a greener, more environmentally friendly and sustainable development, it seems appropriate to emphasize the topic of natural and renewable sources for these compounds. These trends are spurring the demand for research, development and innovation of natural products.[1] Essential oils are one of the most important classes of natural products with application in food, pharmaceutical, cosmetics, fine chemicals and perfumery industries due to their flavor, fragrances and spices. They are also used as precursors in syntheses of new drugs and as sources of complex aromatic derivatives. Per year circa 100,000 tons of volatile essential oils, with a value of about 1 billion US$, are produced worldwide. In 2015, the total world fragrance and flavor market was estimated to be approximately US$ 24 billion, a 33% growth from 2006.[2,3] Besides from the volatile oils, 250,000-300,000 tons of turpentine are also produced, from which about 100,000 tons are used for the production of terpenes such as camphor, camphene, limonene and *p*-cymene.[4] As far as essential oils are concerned, terpenes are the largest and most important class of natural products.

Terpenes have been used since the Egyptians[5] and their importance both in nature and for human related applications is huge. One of the reasons for their widespread use is the abundance and diversity of these compounds; they are found in all living organisms. Using a basic five carbon building block, the isoprene, nature creates an array of compounds with an wide range of structural variations and a vast number of purposes.[6] Many plants as balm trees, caraway, carnation, citrus fruits, conifer wood, coriander, eucalyptus, lavender, lemon grass, lilies, peppermint species, roses, rosemary, sage, thyme and violet, are known due to their aroma, taste and medicinal properties, being terpenes the main responsible for these properties. With more than 55.000 different structures,[7,8] the properties and applications of this class of natural compounds are difficult to overstate. Many of them are considered as GRAS (Generally Recognized As Safe)[9] and their importance makes them attractive to be used in diverse industries as pharmaceutical,[10] food additives,[11] cosmetics,[6] perfumery,[6] fine chemicals[12] and agriculture.[12]

Due to their biological importance and particular properties, the study of these natural products led to the discovery of an enormous variety of useful drugs for the treatment of diverse diseases. In the pharmaceutical field terpenes are used as excipients to enhance skin penetration, active principles of drugs and components of non-prescription drugs.[10] In 2002, the market of terpene-based pharmaceuticals generated about US$ 12 billion.[10] The anticancer taxol and the antimalarial artemisinin are two of the better-known terpene-based drugs.[13] Menthol and camphor are non-prescription drugs widely used in the pharmaceutical field. In 2015, the sales of Salonpas (5.7% menthol and 1.12% camphor),[14] a famous topical analgesic, in the United States reached US$ 60.1 million.[15] In the food industry, terpenes are also very attractive due to their several appealing properties that allow them to be used as safer alternatives to chemical additives.[16,17] The culinary herbs basil, cinnamon, coriander, cumin, lavender, mint, oregano, and rosemary; and trees like eucalyptus, fir and myrtle are famous sources of terpenes.[11] When added to chocolate products, limonene was proposed as a reducer of the fat content and viscosity and therefore its addition can improve the final product quality.[18,19] Fragrances make terpenes and essential oils the most important natural products used by the cosmetic and perfumery industries since ancient times. According to Euromonitor International[20] the beauty industry generated US$ 465 billion in sales in 2014, with a 5 per cent yearly growth, being China and Brazil the most promising markets. This is an evidence that the global demand for cosmetics and perfumes, and consequently essential oils, is still an extremely important and profitable market. There are more than 3000 known essential oils and from these, around 300 are used commercially in the flavor and fragrances market.[16]

Aiming at the development of new applications for this important class of compounds and taking advantage of their hydrophobic character, a part of this thesis is devoted to the attempt to prepare sustainable and cheap hydrophobic solvents from mixtures of terpenes combined with other terpenes or other organic solvents or chemicals – Chapter 2.

For the production of pure terpenes from natural materials,[21] or for the deterpenation, the separation of terpenes is of the utmost importance, being an area regarding eagerly for new technological developments. Thus, to replace noxious organic solvents used in the terpenes production or essential oils deterpenation and to increase the process yield, Chapter 3 investigates the potential of ionic liquids for terpenes fractionation. Moreover, another classes of neoteric solvents, the deep eutectic solvents, are formulated and characterized aiming at the development of new separation processes.

With the advent of the biorefinery, and the increasing importance and volume of terpene production and applications, especially in the fragrance and flavor, pharmaceutical and chemical industries, their environmental impact needs to be considered. Over the last years, the role of terpenes as biogenic volatile organic compounds (BVOC) as well as in aerosol formation became an important topic of research on the chemistry of the atmosphere, with a new emphasis on the ongoing climate change debate.[22–24] It is thought that, on a global scale, volatile organic compounds of biogenic origin exceed by far the amount of anthropogenic emissions, while this is not necessarily true on a regional scale, regarding industrialized and heavily encumbered areas.

In order to contribute to the development of accurate models for the fate of terpenes in the environment, on this thesis a range of physicochemical properties such as densities, water solubilities and critical properties will be accurately measured and/or estimated – Chapter 4. Moreover, water solubilities, vapor pressure and octanol-water partition coefficients can describe a hypothetical chemical space that allows a first screening of compounds with respect to their probable distribution in the environment once released.

The natural emissions of terpenes cannot be targeted for intervention unlike the anthropogenic. Thus, the researchers goal must be the search of strategies and technologies to reduce the environmental impacts of terpenes from biorefineries. For this purpose, aiming at maximizing efficiency and minimizing waste new eco-friendly solvents will be here investigated.

4. Key Innovations

Along this work a novel technique for the solubility measurement of sparingly soluble compounds in water was developed, validated and successfully applied for several compounds. Moreover, aiming at the measurement of activity coefficients at infinite dilution in the University of Aveiro, the experimental procedure used in the Warsaw University of Technology was here implemented for the first time. In the deep eutectic solvents framework, a visual methodology to measure the solid-liquid phase diagrams of mixtures and pure compounds using an automatic glass capillary device was developed and validated. On the other hand, the theoretical approach to estimate the critical properties of terpenes as well as the strategy to test the capability of COSMO-RS to investigate ionic liquids with potential for terpenes fractionation deserves also to be noticed.

5. Applications

Within the framework of neoteric solvents, the work developed investigates the thermophysical properties, phase equilibria and environmental impact of terpenes, as well as ionic liquids and eutectic and deep eutectic solvents. These are relevant for the development of the biorefinery where these compounds and mixtures may play an important role given their interesting properties and applications. In particular, the use of eutectic solvents based on terpenes was already tested in the separation of metals showing very promising results as can be seen in "*Sustainable Hydrophobic Terpene-Based Eutectic Solvents for the Extraction and Separation of Metals, Nicolas Schaeffer, Mónia A. R. Martins, Catarina M. S. S. Neves, Simão P. Pinho, João A. P. Coutinho, Chemical Communications 54, 8104–8107 (2018), DOI: 10.1039/C8CC04152K*". Additionally, the reliable experimental physico-chemical property data measured here are also of enormous importance for direct industrial applications and to the improvement of existent computational methods aiming for properties prediction in such a vast family of compounds.

6. Implementations and Results

The present work reports a comprehensive study on terpenes properties and phase equilibria, that are a contribution for the development of novel terpenes applications, their extraction, and studies addressing their environmental fate.

First, and inspired by the lack of well characterized hydrophobic eutectic mixtures to be used in novel processes and products, sustainable hydrophobic solvents based on terpenes and monocarboxylic acids – and liquid at room temperature – were successfully prepared and characterized. Mixtures between terpenes and monocarboxylic acids form normal eutectic solvents while some mixtures of terpenes form the so called deep eutectic solvents.

To be used in different applications pure terpenes must be extract from essential oils and subsequently fractionated, and ionic liquids were here evaluated to that purpose. Results show that ILs may replace conventional entrainers applied for the separation processes of aliphatic/aromatic hydrocarbons and, concerning terpenes the most effective ILs would require polar anions to improve selectivity and non-polar cations to increase capacity. Based on the later conclusions, it was decided to design deep eutectic solvents for the same purpose. Ammonium salts were combined with fatty alcohols or fatty acids and novel DES and simple eutectic mixtures designed and their solid-liquid phase diagrams characterized and modeled.

When envisaging large-scale applications terpenes will inevitably end in the environment. Anthropogenic releases allied to their natural emissions are concerning the environmentalists. In this context, the solubilities of terpenes in water were determined confirming their hydrophobicity and a set of critical properties was estimated and recommended. A derived two-dimensional plot describing a hypothetical chemical space shows that in general and despite their low solubility in water, terpenes are partitioning into the three environmental compartments.

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