Type V Deep Eutectic Solvents: Design and Applications

Dinis O. Abranches¹ and João A. P. Coutinho¹*

¹CICECO - Aveiro Institute of Materials, Department of Chemistry, University of Aveiro, Aveiro, Portugal.

*Corresponding Author: João A. P. Coutinho (jcoutinho@ua.pt)

Abstract

Type V deep eutectic solvents are a novel class of sustainable solvents. They are prepared by physically mixing solid, non-ionic components and are characterized by strong negative deviations from thermodynamic ideality. This work provides guidelines for the rational design of these solvents and reviews some of their recent applications. Emphasis is given on the choice of hydrogen bond donors and acceptors to achieve the necessary liquid phase non-ideality, namely on the use of pairs of molecules with high polarity asymmetry, and stresses the importance of assessing their solid-liquid phase diagrams. Polymorphism and cocrystal formation are also briefly addressed, together with predictive methodologies that have been developed to estimate their properties.

Keywords: Green Solvents | Hydrogen Bonding | Solid-Liquid Equilibrium | Terpenes | Thymol | Trioctylphosphine oxide
1. Introduction

Eutectic solvents (ESs) are a class of novel green solvents with a wide range of properties and applications [1–5]. While most solvents are pure substances, ESs are liquid mixtures prepared by mixing solid components. Their liquid phase arises due to the solid-liquid equilibrium (SLE) established between their precursors, leading to the formation of eutectic-type systems with significant melting temperature depressions. Because ESs are mixtures, their properties can be easily tailored by carefully choosing their precursors and relative composition.

Although these terms are often used interchangeably, deep eutectic solvents (DESs) are ESs whose components present significant negative deviations from thermodynamic ideality [6]. These negative deviations lead to steeper melting temperature depressions, hence the prefix deep, and occur when the intermolecular (non-covalent) interactions in the DES are stronger than those present in the liquid phases (hypothetical or not) of the pure precursors. As such, rather than measuring the melting temperature of a single mixture with a specific mole ratio, it is fundamental to measure the entire SLE phase diagram of a system before classifying it as a DES [6–8].

DESs are commonly prepared by mixing hydrogen bond donors (HBDs) with hydrogen bond acceptors (HBAs) and are classified into five different types (I–V). Unlike types I–IV, the recently proposed type V DESs [9] are prepared using solely non-ionic precursors. As such, they typically display lower viscosities than their ionic counterparts [10–12], non-negligible vapor pressures (may be advantageous for processes where solvent evaporation is desirable) [13,14], and are chloride-free. Furthermore, while the design of hydrophobic types I–IV DESs is limited to the use of ions with large apolar volumes [15], there is ample choice of non-ionic substances that can be used to prepare type V DESs with different degrees of hydrophobicity [16–18].

The main goal of this perspective is to review recent works in the field where type V DESs where designed and applied. Throughout the work, guidelines are introduced towards the design of these novel solvents, focusing on the importance of polarity asymmetry in the HBDs and HBAs chosen. The polymorphism of some of these systems is also examined, as well as thermodynamic models that can be used to screen possible precursors. The main key topics covered in this work are illustrated in Figure 1.
Figure 1. Model examples of solid-liquid phase diagrams for ideal and non-ideal systems, highlighting mixtures of regular HBDs and HBAs, as well as asymmetric HBDs and lone HBAs. Non-ideality can be assessed by the difference between the ideal and experimental SLE diagrams. Cocrystal formation is also illustrated.
2. Designing Towards Non-Ideality

The presence of hydrogen bonding in a mixture does not necessarily lead to negative deviations from ideality. Instead, regardless of their type, the intermolecular interactions in the DES must be stronger than those present in the liquid phases (hypothetical or not) of the pure components. In this way, reliable precursors to prepare type V DESs include asymmetric HBDs and lone HBAs, which will be discussed below. Note that the term asymmetric is being used to describe HBDs that possess strong HBD but weak HBA sites (thus displaying asymmetric polarity) and should not be confused with structural or configurational asymmetry.

2.1 Asymmetric Hydrogen Bond Donors

Common HBDs (e.g. alcohols, acids, and amines) also contain hydrogen bond acceptor sites. Thus, they already establish hydrogen bonding in their pure phases and usually behave ideally when mixed with HBAs, hampering the formation of type V DESs. An exception to this are asymmetric HBDs, such as thymol in the prototypical type V DES thymol/menthol [9]. Due to resonance effects, the hydroxyl group of thymol is more positive than usual (Figure 2). This leads to a stronger HBD but weaker HBA site, hence the use of the term asymmetric. Thus, thymol can only establish a hydrogen bond with itself between a stronger HBD site and a weaker HBA site. However, if mixed with a regular HBA, thymol can now establish a hydrogen bond between its stronger HBD site and the regular HBA site of the second component. Because this hydrogen bond is stronger than that of thymol-thymol or menthol-menthol, a type V DES is formed.

The polarity asymmetry of thymol is exemplified in Figure 2 by comparing the SLE phase diagrams of thymol-based systems and menthol-based systems. Note the structural similarity of thymol and menthol, and how menthol does not have the polarity asymmetry of thymol. This leads to negative deviations from ideality in the thymol-based systems (seen by the difference between the experimental and ideal SLE phase diagrams), while menthol-based systems behave ideally (seen by the overlap of the experimental and ideal SLE phase diagrams). As such, thymol/hexadecanoic acid and thymol/camphor may be classified as type V DESs, while menthol/hexadecanoic acid and menthol/camphor are eutectic solvents.
Several terpenes possess the resonance effect and consequent polarity asymmetry discussed above and they are the most investigated compounds when designing type V DESs [22–26], with emphasis given to thymol/menthol. For example, Santana-Mayor et al. [27] used it to develop an analytical methodology for the microextraction of phthalic acid esters and Silva et al. [28] employed it to extract triterpenic acids (ursolic acid, oleanolic acid, and betulinic acid) from *Eucalyptus globulus* bark. Other examples of phenolic-based type V DESs include butylated hydroxytoluene/menthol [29], which retains the antioxidant properties of butylated hydroxytoluene, thymol/decanoic acid [30], which was studied as an absorbent for volatile organic compounds, and several drug-based systems [31].

The study of the SLE phase diagrams of eutectic solvents, advocated in this work, provides knowledge not only on the non-ideality of the systems (allowing their classification as *deep*), but also on their liquid window. This can be used to tailor the properties of the solvent by changing the mole fractions of its...
constituents. For example, the properties of thymol/camphor were shown to be easily tuned by simply adjusting its composition within its liquid window at room temperature (between a camphor mole fraction of 0.2 and 0.7) [20]. Kamlet-Taft parameters were particularly flexible, with $\alpha$ ranging from 0.6 to 0.9, $\beta$ from 0.6 to 0.8, and $\pi^*$ from 0.5 to 0.2.

There are exceptions to the extraordinary DES-forming ability of thymol. For instance, its mixture with fatty acids leads to thermodynamic ideal systems [19,32]. The asymmetry in the acidity observed between the thymol and alcohols is lost in the thymol-carboxylic acid systems. It is also worth noting that the polarity asymmetry needed to prepare type V DESs is not limited to phenolic molecules. For example, Marchelli et al. [33] demonstrated the polarity asymmetry of hexafluoroisopropanol (HFIP) in systems composed of HFIP and acetone, revealing stronger hydrogen bonding in the mixture rather than the pure compounds. Cabaço et al. [34] showed that the dominant intermolecular interaction in mixtures of tert-butanol (TBH) and perfluoro-tert-butanol (TBF) is a hydrogen bond between the HBD site of TBF and the HBA site of TBH. Both results indicate that the electron withdrawing effect of fluorine leads to hydroxyl groups with stronger HBD but weaker HBA capabilities, similarly to the effect that aromatic resonance has on thymol. This suggests that fluorinated compounds, namely fluorinated alcohols, may be used as type V DES-forming HBDs. Deng et al. [35] explored this concept by mixing HFIP with L-carnitine or betaine, yielding liquid mixtures at room temperature that were used for liquid-liquid microextraction of pyrethroids from complex matrices. Note, however, that the classification of zwitterion-based DESs as type V or type III is unclear.

2.2 Lone Hydrogen Bond Acceptors

Another reliable way of preparing type V DESs is to use HBAs that do not possess HBD sites (e.g. ketones, aldehydes, and ternary amines). This type of compound will be referred throughout this work as lone hydrogen bond acceptors. Because they cannot establish hydrogen bonds with themselves, these molecules usually display negative deviations from ideality when mixed with common HBDs, leading to the formation of type V DESs. For instance, Liu et al. [36] used 1,5-diazabicyclo[5.4.0]-5-undecene (a cyclic compound with two aprotic nitrogens functioning as hydrogen bond acceptor sites) to prepare several type V DESs with a plethora of different HBDs. Albeit there is no information on the non-ideality of these systems, cyclodextrins may also be type V DES-forming compounds owing to their large amount of HBA sites [37,38]. Betaine, which is a zwitterion compound, has also been shown to be a universal HBA for the reasons mentioned above [39], but the classification of betaine-based DESs as type V is unclear, as mentioned in the previous section.

Triocylphosphine oxide (TOPO) is an excellent example of a lone HBA that consistently yields type V DESs when mixed with regular HBDs. This is illustrated in Figure 3 by depicting the SLE phase diagrams of the systems thymol/TOPO, menthol/TOPO, dodecanoic acid/TOPO, and dihexylurea/TOPO. Note that thymol is a DES-forming HBD (as discussed in section 2.1), while TOPO
is a DES-forming HBA. Thus, thymol/menthol and menthol/TOPO are both type V DESs with significant liquid phase non-ideality, but menthol acts as a HBA in the former and as a HBD in the latter. Also, note that TOPO, unlike thymol, is able to form type V DESs with fatty acids.

![Figure 3. Solid-liquid phase diagrams of the systems thymol/TOPO (top left corner) [40], menthol/TOPO (top right corner) [41], dodecanoic acid/TOPO (bottom left corner) [42], and dihexylthiourea/TOPO (bottom right corner) [42]. Full lines represent the ideal solid-liquid phase diagrams while dashed lines are visual guides. The chemical structures of the compounds are included as insets.](image)

Given its remarkable complexation ability, TOPO has been the most widely researched lone HBA in type V DES literature. For example, Vargas et al. [43] investigated the ability of decanoic acid/TOPO to separate platinum and palladium from acidic aqueous solutions, Van den Bruinhorst et al. [42] used dodecanoic acid/TOPO and dihexylthiourea/TOPO to extract volatile fatty acids (acetic, propionic, and butyric acids), Brouwer et al. [41] applied thymol/TOPO and menthol/TOPO as liquid-liquid extractants of several bio-based chemicals, Lalikoglu [44] prepared menthol/TOPO to separate butyric acid from aqueous media, and Gilmore et al. [45] demonstrated the exceptional extraction efficiency of uranyl from acidic aqueous solutions provided by phenol/TOPO.

The use of lone hydrogen bond acceptors to prepare type V DESs connects not only to their melting temperature, but also to their viscosity. Fan et al. [10] showed that DESs based on precursors possessing only one HBD/HBA site led to low viscous systems, while the use of precursors with several HBD/HBA sites (e.g. acids) resulted in the formation of strong hydrogen bonding networks that severely increased
the viscosity of the final mixture. This hints at the advantages of designing type V DESs using lone HBAs, but further investigation is necessary.

2.3 Beyond Hydrogen Bonding

The design strategies and works discussed above relied on the use of hydrogen bonding to achieve negative deviations from ideality and significant melting temperature depressions. However, there are other types of non-covalent interactions that can be exploited, namely halogen or chalcogen bonding (otherwise known as pnicogen bonds, σ-hole bonding, and π-hole bonding [46,47]). This was first proposed by Peloquin et al. [48], who showed that the system dithiane/iodofluorobenzene is a type V DES, with the non-ideality arising from the formation of strong halogen bonding between the components. Although not referred to as such by the authors, the henoyltrifluoroacetone/TOPO type V DES prepared by Hanada and Goto [49] may be another example of this phenomenon.

3. Cocrystals and Polymorphism

The main design philosophy adopted so far is that the precursors of type V DESs should establish stronger interactions when mixed than when pure. This is a useful rule of thumb, but there are instances where this framework fails. One such case is when intermediate compounds such as cocrystals are formed, as exemplified in Figure 4.

![Figure 4. Solid-liquid phase diagrams of the systems phenol/pyridine (top left corner), phenol/quinoline (top right corner), o-cresol/pyridine (bottom left corner), and 2-chlorophenol/pyridine (bottom right corner). Full lines represent experimental data points, and dashed lines represent theoretical predictions.](image-url)
represent the ideal solid-liquid phase diagrams while green data points highlight the formation of intermediate compounds. The chemical structures of the compounds are included as insets. Data taken from Bramley [50].

Ignoring toxicity issues and the fact that some of these compounds are already liquid well below room temperature, phenol, o-cresol, and 2-chlorophenol are excellent model molecules of asymmetric hydrogen bond donors, while pyridine and quinoline are lone hydrogen bond acceptors. However, as the phase diagrams depicted in Figure 4 reveal, their mixtures result in the formation of cocrystals. Near the pure compositions, the experimental SLE behaves as expected, with strong negative deviations from ideality. However, when the cocrystal is formed, there is a sharp increase in the melting temperature, which would hamper the applicability of these systems as type V DESs.

Many type V DESs display polymorphism issues, including the prototypical thymol/menthol system. In fact, Minceva and coauthors [51,52] provided a detailed analysis of its solid-liquid equilibrium and found the formation of intermediate compounds, namely two cocrystals with thymol/menthol mole ratios of 3:1 and 3:2, and two solid solutions near the 3:1 mole ratio. However, due to the overall poor crystal packing of thymol and menthol (the isopropyl group of thymol provides some non-planarity to the molecule while menthol is fully non-planar), these polymorphs are not particularly stable and decompose at low temperatures, having little impact on the SLE diagram or the overall melting temperature of the system. As such, cocrystal formation and the consequent hampering of the melting temperature depression effect can be mitigated by choosing HBDs and HBAs with poor packing characteristics [53]. For aromatic compounds, this translates into the use of alkyl chain substituents. Other examples of polymorphism in type V DESs include dithiane/iodofluorobenzene [48] and the system bonerol/camphor, which produces a solid-solid solution [20].

4. Predictive Models

The most successful predictive methodology for the SLE phase diagrams of type V DESs is the COSMO-RS thermodynamic model, which was used in several of the works mentioned above [12,20,22,24,26,30,31,41,51]. Because COSMO-RS is able to predict the chemical potential (and activity coefficients) of the components in a mixture, it is an excellent screening tool to guide the experimental design of type V DESs. Furthermore, COSMO-RS can also be used to evaluate the solubility of target molecules in DES. For example, Fan et al. [54] used COSMO-RS to design a type V DES for the extraction of lutein from microalgae. To do so, the authors initially used the model to screen several binary combinations by predicting their SLE phase diagrams. Then, the infinite dilution activity coefficient of lutein was estimated in the mixtures with lower melting temperatures, finally arriving at thymol/fenchyl alcohol as the best type V DES for the extraction of this solute.

Other predictive methodologies beyond COSMO-RS have been proposed. Hou et al. [55] developed a group contribution model to predict the melting temperature of DESs (types I-V). The model was trained on a database of 1541 data points and presented a mean relative error of just 5.7%. Even more
remarkable, because the model was trained based on mole fractions, rather than considering DESs as mixtures with a fixed mole ratio, they were able to predict solid liquid phase diagrams of DESs in their entire composition range. The same research group developed a similar group contribution model for densities, attaining a mean relative error of 1.49% for the training set and 1.56% for the testing set [56]. Finally, Zamora et al. [12] used machine learning to correlate and predict the density and viscosity of several type V DESs, attaining root mean square errors of 0.02 g/mL and 14.4 mPa∙s for the testing sets of density and viscosity, respectively. The scarcity of experimental data prevented the authors from applying this methodology to other properties, namely melting temperature.

**Conclusions and Future Work**

This work provides a simple framework to rationally choose solid compounds to use in the formation of type V DESs. It is important to emphasize that the cornerstone of DES design is the ability to liquefy a compound with a desired property (e.g. complexation ability), so that it can be used as a liquid solvent. This target compound may already be an asymmetric HBD or lone HBA, as exemplified by thymol and TOPO, in which case it can be liquefied using a myriad of regular HBDs and HBAs, or may be a regular HBD/HBA, as exemplified by menthol, in which case an asymmetric HBD or lone HBA should be used for its liquefaction. The formation of polymorphs has a negative effect upon the melting temperature depression phenomenon that could be avoided by using molecules with poor crystal packing characteristics, as illustrated by the thymol/menthol system.

Going forward, emphasis should be given on measuring SLE phase diagrams of eutectic solvents, not only to assess their non-ideality and their liquid window, but also to avoid incorrect assessments of the melting temperature depression. For instance, a system may form a cocrystal at a 1:1 mole ratio but possess significant melting temperature depression near the pure compositions that can yield liquid mixtures. Predictive screening methodologies are available, namely COSMO-RS, which can be used to estimate the SLE phase diagrams of potential DES-forming precursors. Interest in computational simulations and machine learning is growing, but more experimental data is needed.

**Acknowledgments**

This work was developed within the scope of the project CICECO-Aveiro Institute of Materials, UIDB/50011/2020 & UIDP/50011/2020, financed by national funds through the Portuguese Foundation for Science and Technology/MCTES.
References


** First proposal of type V DESs, including thymol/menthol. Explains the polarity asymmetry
of thymol through resonance effects and rationalizes its impact on the non-ideality of several thymol-based systems. Proposes other asymmetric HBDs and lone HBAs using a COSMO-RS screening.


* Extensive collection of data (particularly density, viscosity, and melting points) and applications of hydrophobic eutectic solvents, some of which may be classified as type V DESs.


* Good example of a COSMO-RS-guided solvent design for furfural production. The authors use COSMO-RS to estimate the infinite dilution coefficient of furfural in several solvents, some of which type V DESs. The best hits are then probed experimentally.


* This work uses the type V DES thymol/menthol to develop an analytical methodology for the microextraction of phthalic acid esters from water samples of environmental concern. The methodology was shown to have remarkable sensitivity, achieving a lower limit of quantification between 0.013 and 0.425 μg/L, depending on the phthalate analyzed.


* Type V DESs based on the lone HBD 1,5-diazabicyclo[5.4.0]-5-undecene are shown to efficiently dissolve lignin, retaining the properties of the starting compound. Furthermore, solvent design flexibility is illustrated by measuring the Kamlet-Taft solvatochromic parameters of the DESs at different mole fractions and using different HBDs, which are then used to maximize lignin solubility.


** First proposal of the use of halogen bonding to prepare type V DESs. The melting temperature of several mixtures of dithianes and iodofluorobenzenes are initially measured at the ideal eutectic composition, revealing negative deviations from ideality in the 1,3-dithiane/1,2-diiodo-3,4,5,6-tetrafluorobenzene system. The SLE phase diagram of this system is also assessed, and some cocrystals are identified.


[52]** A. Alhadid, C. Jandl, L. Mokrushina, M. Minceva, Experimental Investigation and Modeling

** Thorough investigation of the SLE phase diagram of thymol/menthol, where two cocrystals and two solid-solid solutions were, for the first time, identified and characterized.


* A robust group contribution method is proposed in this work to predict the melting temperature of DESs. The model uses different parameters depending on the type of DES (I-V) and was trained using composition as an input. Therefore, the model is also capable of predicting entire SLE phase diagrams.


• Type V deep eutectic solvents are versatile green solvents with tremendous design flexibility
• Thermodynamic non-ideality is best attained by pairing asymmetric HBDs with lone HBAs
• Thymol, HFIP, and salicylic acid are examples of asymmetric HBDs
• TOPO, DBA, and betaine are examples of lone HBAs
• Polymorphism can be mitigated by choosing molecules with poor crystal packing
• COSMO-RS and group contribution methods are feasible phase diagram predictors
Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: