Big Data for a Deep Problem: Understanding the Formation of NADES Through Comprehensive Chemical Analysis and RDKit

Lucas B. Ayres, Grayson Weavil, Mays Alhoubani, Barbara G. S. Guinati, and Carlos D. Garcia*

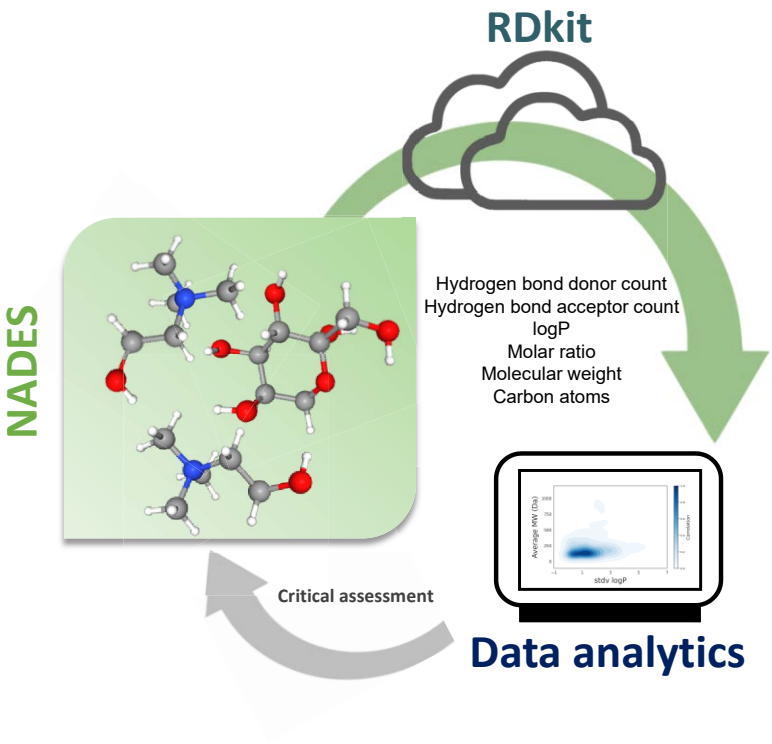
Department of Chemistry, Clemson University, Clemson SC 29634, USA

* To whom correspondence should be addressed. 211 S. Palmetto Blvd, Clemson, SC, 29634, United States, e-mail: cdgarci@clemson.edu

ABSTRACT

This manuscript offers an in-depth analysis of Natural Deep Eutectic Solvents (NADES) reported over the past decade, derived from an expansive database encompassing 1334 NADES formulations. Key insights generated from this analysis underline the critical role of choline chloride as the predominant hydrogen bond acceptor, and the need for a careful balance in favor of hydrogen bond donors. Furthermore, the analysis underscores the pivotal role played by small molecules (over polymers) in the successful formation of NADES. Considerations around the careful selection and compatibility of NADES components are emphasized, as well as potential complications associated with the incorporation of water, which could potentially destabilize the hydrogen bond network of these eutectic mixtures. This study serves as a guide for researchers to navigate the complex landscape of NADES design and application, acknowledging the remaining challenges and opportunities in this promising field.

GRAPHICAL ABSTRACT



1. INTRODUCTION

The last ten years have witnessed an exponential increase in scientific research featuring Natural Deep Eutectic Solvents (NADES) [1-11]. These solvents were initially described as a distinct group of liquids found within plant tissues, displaying a significant role in their biochemistry [12], especially in the transport of compounds with medium polarity. After substantial research efforts, it is now known that NADES are formed by precise combinations of two or three natural components, usually in the solid state that, upon heating, result in a substance with a significantly lower melting point than the individual components. Out of those, perhaps the most interesting combinations are those considered *stable* NADES, those that remain liquid for at least a week when stored at room temperature. As shown in Figure 1, these novel solvents feature significant advantages over traditional organic solvents [13-15], ionic liquids [16, 17], and traditional (non-natural) DES [18, 19]; including the claimed eco-friendly aspect of their components, which are primarily natural molecules such as sugars [20], amino acids [21], alcohols [22], carboxylic acids [23], etc. In an ideal scenario, the broad range of physico-chemical attributes inherent to the structure of those natural components should direct the design of NADES with adjustable properties such as conductivity, melting point, stability, polarity, and viscosity [24]. However, the multifaceted properties of each component (*e.g.*, hydrogen bond donor count, hydrogen bond acceptor count, molecular weight, surface area, melting point, hydrophobicity, etc.) pose considerable challenges to the rational development of NADES with specific characteristics. In fact, the discovery and optimization of these solvents predominantly rely on empirical approaches, reflecting the complexity of this problem.

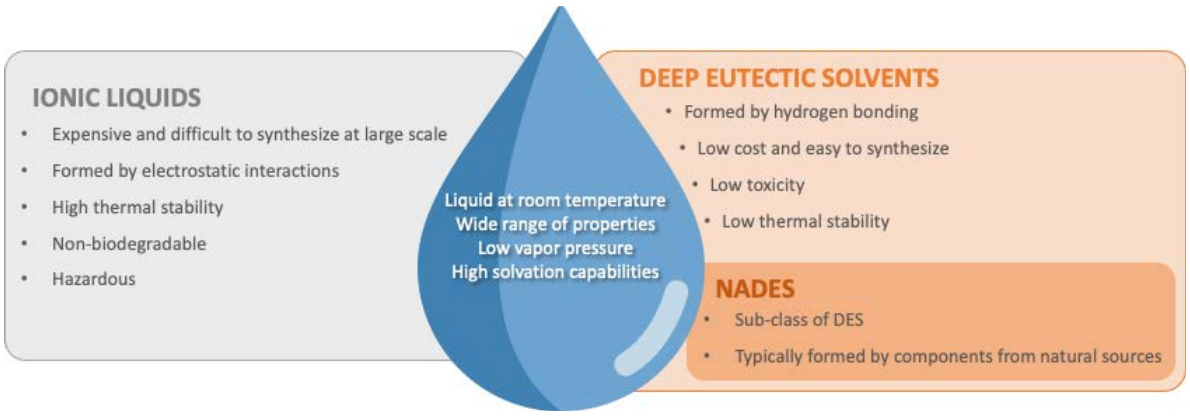


Figure 1: Comparison between ionic liquids, deep eutectic solvents and natural deep eutectic solvents.

While many researchers subscribe to the idea that the formation of NADES is driven by the formation of a hydrogen bond network [25], understanding the intricate interplay of variables involved in these reactions remains a challenge. Aiming to gain a detailed understanding of the molecular interactions supporting the formation of these solvents, researchers have presented multiple computational approaches [25-28], including those based on density functional theory (DFT) [29-32], molecular dynamics (MD) [33], and machine learning methods [34-36]. Although these approaches can provide useful insights for selected NADES properties, these studies are typically limited to a handful of compounds and (unfortunately) do not provide rational guidelines to understand the behavior or other NADES, exploring the diverse chemical landscape of natural molecules. Moreover, as it will be discussed later, many of the reports provide conflicting information, that cannot be extended outside the specific experimental variables reported.

Knowing the potential of these solvents for research and industry, we herein present a general analysis of the NADES included in a recently released database [37]. This repository includes almost 1500 examples of NADES, along with multiple properties that provide a general and representative overview of the field. Rather than reporting on specific systems, the presented analysis is intended to focus on “what has worked” so far, serving as a general guide for researchers working with NADES.

2. MATERIAL AND METHODS

2.1. NADES database. The initial chemical dataset was developed based on an extensive literature review published by Omar and Sadeghi in 2022 [37]. The stoichiometric ratios of the reported NADES were retrieved from the original manuscript using a python script, leading to a data frame containing the name of hydrogen bond acceptor, the name of the hydrogen bond donor, the molar ratio, and (if reported) the corresponding melting point, density, viscosity, conductivity, surface tension, and refractive index. This database was stored in a csv file (non_aug_nades_2023.csv). It is important to point out that unstable formulations (leading to the formation of a precipitate within one week) were not transferred to our initial database, that included approximately 1332 formulations of binary and tertiary NADES.

2.2. Augmented NADES database. In order to include relevant chemical information, the original database was augmented using RDKit, an open-source cheminformatics software toolkit designed for working with small molecules. Toward this goal, all the hydrogen bond donor and acceptor molecules were first converted (from their chemical name) into canonical SMILES using PubChemPy[a] (v.1.0.4). Then, the resulting SMILES notations of each component on each NADES reported were used to expand our database through the open source RDKit Python[b] (v.2022.03.3) application programming interface (API). We selected only relevant chemical descriptors pertinent to the NADES context, including: number of atoms, number of heavy atoms, polar surface area, molecular weight, number of aromatic rings, number of heteroatoms, logP, number of carbon atoms, number of oxygen atoms, number of nitrogen atoms, and number of chloride atoms. It is worth mentioning that the hydrogen bond donor count and hydrogen bond acceptor count were queried using PubChemPy, due to inconsistencies between the values retrieved by RDKit with respect to those published in the literature. Pertinent calculations (such as average, standard deviation, addition, and multiplication) were performed directly on the augmented database and new columns were added for each operation. As a result, the final proprietary NADES database contains approximately 80.000 data points that provide a much richer chemical information [38].

2.3. Data analytics. The analyses presented in this manuscript were performed directly in Python through the use of statistical data visualization libraries such as Seaborn (v. 0.12.2). The bibliometric analysis was performed using the Clarivate Web of Science database. The results were stored in csv format and used in Research Rabbit, to generate the literature network for the most relevant publications for this field.

3. RESULTS AND DISCUSSION

The following sections aim to provide a critical assessment of selected features (e.g., most common formulations, effect of molecular weight, logP, hydrogen bond donor/acceptor and count, and effect of water additions) of the NADES present in our database, and in the context of pertinent literature reports. We also briefly discuss other important properties and how those variables could potentially impact future

[a] https://pubchempy.readthedocs.io/

[b] https://www.rdkit.org/docs/GettingStartedInPython.html

developments in the field. It is worth mentioning that our analysis does not to provide a detailed discussion of the fundamental aspects of NADES, as this information can be found elsewhere [9, 39, 40]. In-depth comparisons between NADES and alternative mediums such as ionic liquids and DES can be found in previously-reported manuscripts [16-19].

3.1. Bibliometric analysis. NADES are a promising sub class of deep eutectic solvents (DES) that collectively feature unique properties (Figure 1) and that have opened new research opportunities. Since they were first identified, the number of publications specifically describing NADES has been exponentially increasing (Figure 2A), currently accounting for approximately 35% of all reported publications related to DES. This percentage is projected to further increase, reaching approximately 43% of the field by the end of this year. This growth highlights the increasing prominence of NADES within the research community and more specifically within the field of eutectic mixtures. Aiming to delve into the most significant contributions, Figure 2B provides insights into the 50 most cited papers (represented by green circles) and their relation with similar works (represented by blue circles). This visualization not only shows the interconnected nature of the research groups working in the NADES domain but also how cross-referenced the work is. The latter be considered a double-edged sword, as not only new ideas but also misconceptions could easily spread in this tight scientific network.

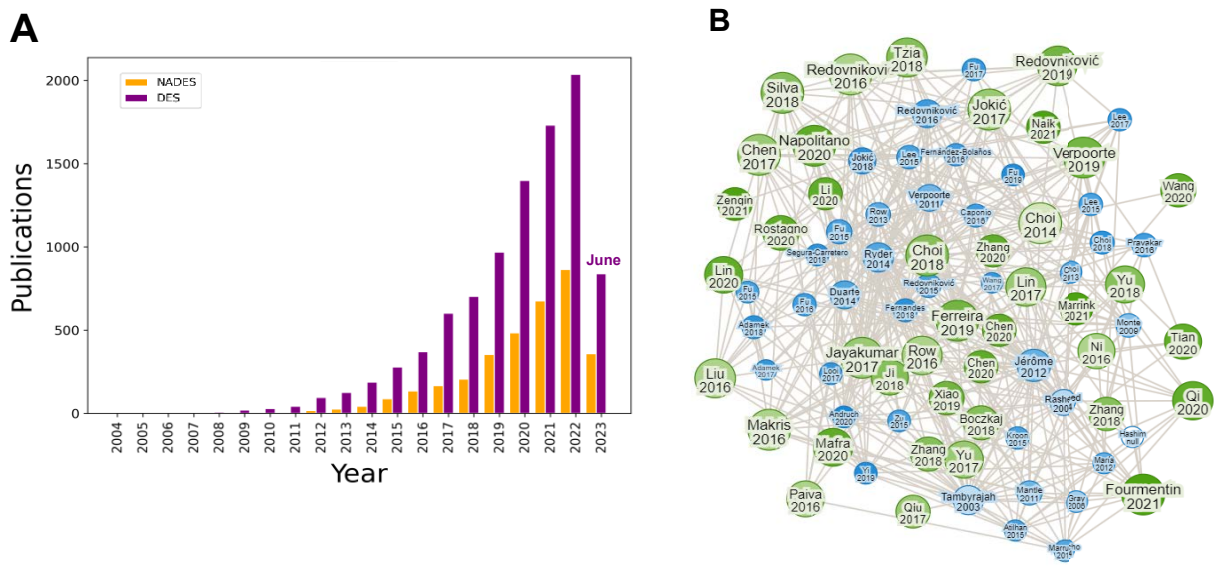


Figure 2: A: Number of publications for NADES (orange) and DES (purple) ranging from 2004 to June 2023. B: Top 50 most cited authors (green) and other relevant works (green).

3.2. Most common NADES formulations and constituents. A first analysis of the database published by Omar and Sadeghi [37] shows that most of the NADES reported correspond to mixtures involving two components (1195, 90%). Among those, NADES composed of betaine and glycine (10.3%) as well as mixtures of choline chloride with glycine (22.4%), coumaric acid (10.3%), ethylene glycol (10.3%) and phenol (9.3%) are the most commonly reported (Figure 3A). Far behind, are mixtures including one hydrogen bond acceptor and two types of hydrogen bond donors (137, 10%). Among those, the most commonly reported NADES include mixtures of choline chloride, coumaric acid, and ethylene glycol (20.8%), betaine, glycine, and L-arginine (12.5%), and choline chloride, glycine, and ethylene glycol (12.5%) (Figure 3B).

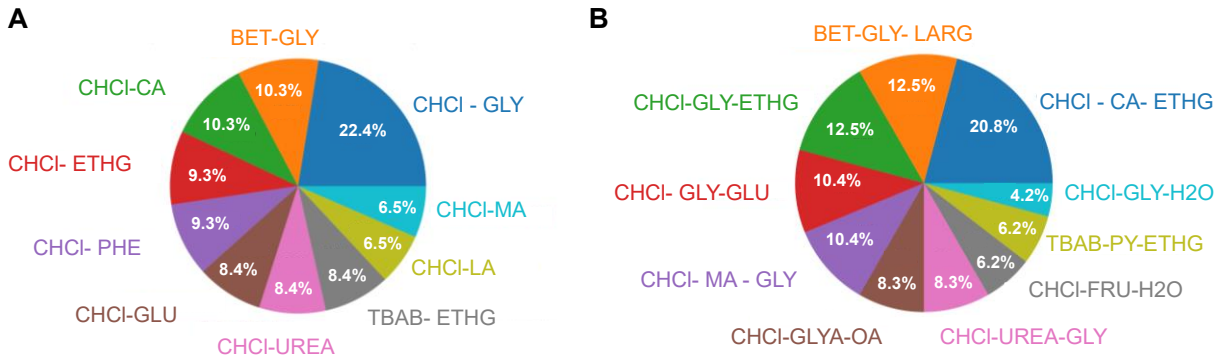
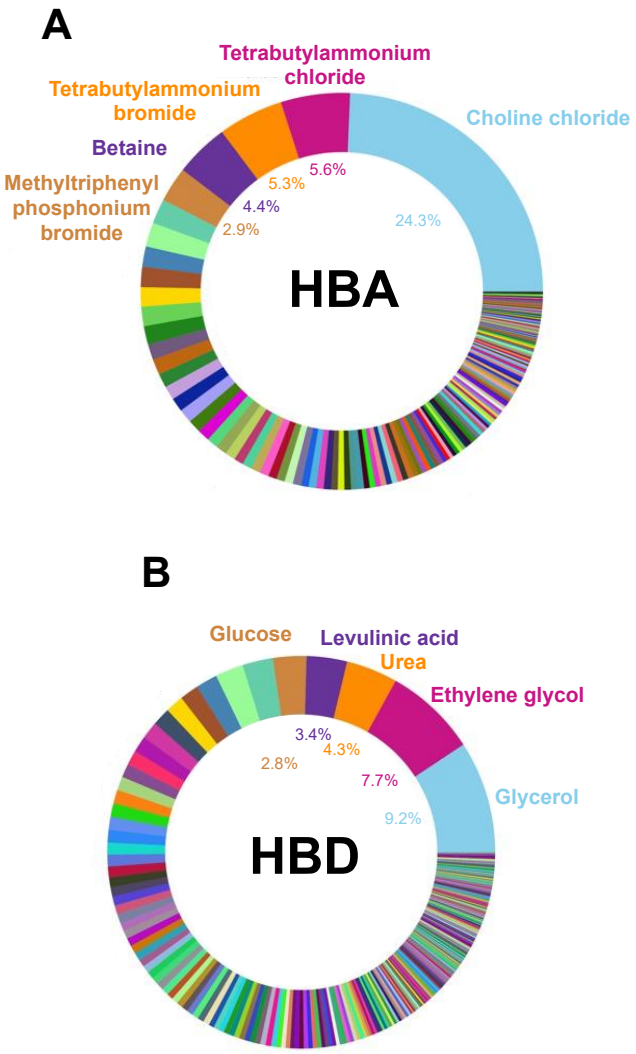


Figure 3: Top 10 most common binary (A) and tertiary (B) NADES formulation reported in the literature. List of abbreviations: **CHCl:** Choline chloride; **GLY:** Glycerol; **BET:** Betaine; **CA:** Caffeic acid; **ETHG:** Ethylene glycol; **PHE:** Phenol; **GLU:** Glucose; **TBAB:** Tetrabutylammonium bromide; **LA:** Lactic acid; **MA:** Malic acid; **LARG:** L- arginine; **OA:** Oxalic acid; **FRU:** Fructose; **PY**: Pyridine

When broadening this analysis to include all NADES formulations reported over the last two decades, authors have reported NADES containing only 166 unique compounds acting as hydrogen bond acceptors (Figure 4A). Among those, choline chloride emerges as the most reported (24.3% of the NADES formulations), followed by tetrabutylammonium chloride/bromide (10.9%), betaine (4.4%), methyl triphenyl phosphonium bromide (2.9%), and menthol (2.0%). The tendency of relying on choline chloride as HBA can be attributed to its exceptional capacity to form hydrogen bonds [41], charge asymmetry [39] and molecular geometry. However, despite claims of the natural origin of this compound [42], the industrial synthesis of choline chloride typically involves the use of traditional reagents (e.g., hydrogen chloride, trimethylamine, and ethylene oxide), leading to the generation of toxic waste; which seems to be in conflict with the associated green aspects of these solvents [43].

On the other hand, glycerol (9.2%), ethylene glycol (7.7%), urea (4.3%), levulinic acid (3.4%), and glucose (2.8%) are the most common hydrogen bond donors in the analyzed NADES formulations (Figure 4B). Last but not least, the most commonly reported ternary NADES were formed using water (28.7%), ethylene glycol (16.9%), and glycerol (9.6%). It is important to mention that for the sake of accuracy, this analysis is exclusively based on the categorization reported in the original database [37], which considers the third component as a hydrogen bond donor used to modify the viscosity of the resulting NADES and that can include other molar ratios [40]. It is also important to note that while many of these compounds are already liquid at room temperature, the formation of the NADES largely exceeds the solubility limits of those mixtures and has been extensively investigated [40, 44-46], beyond the simple stability test [47, 48].



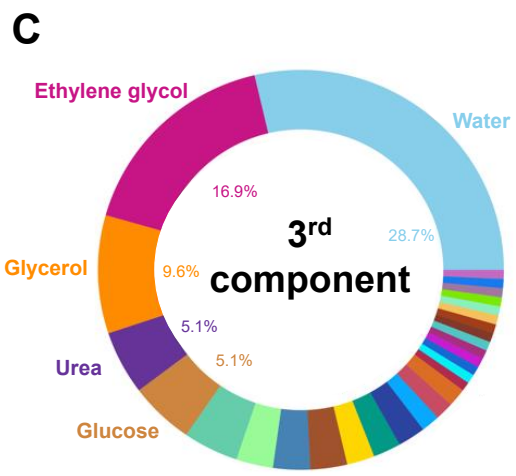


Figure 4: Relative percentage of hydrogen bond acceptor group (HBA) (A), hydrogen bond donor group (HBD) (B) and 3rd component (C) in NADES formulations.

It is also important to note that the chemical diversity of these molecules has allowed researchers to move far beyond the simple 1:1 mixtures (out of which the most common is 1:2, 24% of the reported NADES). In fact, and noting the large standard deviation of the results, the average number of moles of the compound used as HBA is 1.5 ± 1.5, and the average number of moles of the compound used as HBD is 2.5 ± 2.

3.3. Units of hydrogen bond acceptors (HBA) and hydrogen bond donors (HBD). It is well-accepted that hydrogen bond interactions contribute to the formation and stability of these solvents, affecting their physical and chemical characteristics [49]. While it is true that there is no universally-optimal balance between the number of moles of HBA and HBD is required to either form a NADES nor to provide specific properties, it is important to consider the overall composition of the reported systems. It is also worth noting that the number of hydrogen bonds that an individual molecule can form, and the strength of those interactions can vary widely, depending on the specific molecular environment [50]. Considering the complexity of this problem, we focused our analysis on the total number of hydrogen bond units in each of the reported NADES combinations. This magnitude was calculated considering the number of moles involved in the corresponding NADES (n), times the number of hydrogen bond count per molecule (C, as reported in PubChem). For example, a NADES formed by mixing 1 mol of choline chloride (n_{HBA}=1) and 1 mol of urea (n_{HBD}=1) was computed considering involving 2 hydrogens bond acceptor counts (C_{HBA}=2) and

2 hydrogens bond donor counts (C_{HBD}=2). This analysis allowed us to analyze the molar ratios reported in the database, in the context of their own chemical nature. The results of the analysis for binary combinations are shown in Figure 5A and Figure 5B.

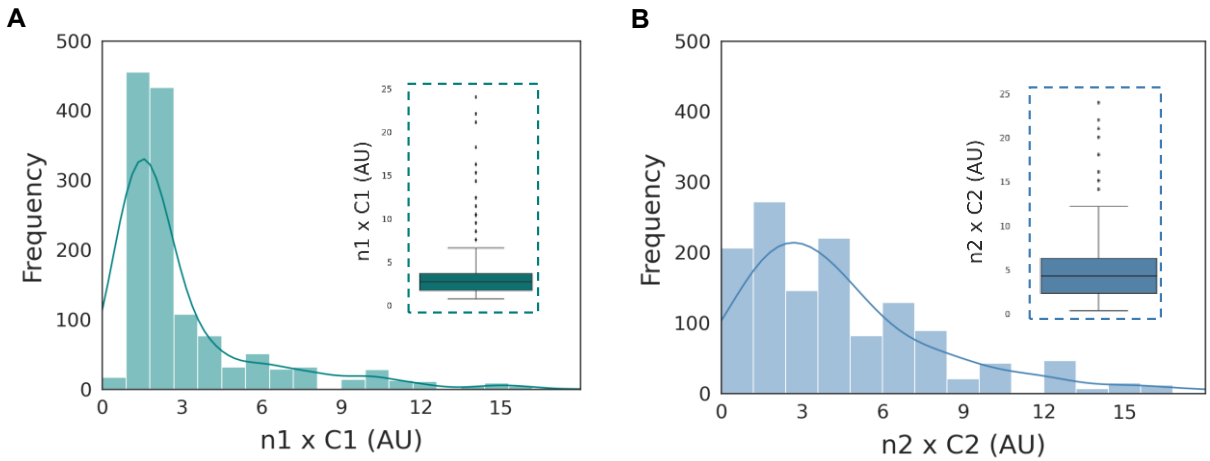


Figure 5: Frequency distribution of the hydrogen bond acceptor count x its number of moles (A) and hydrogen bond donor count x its number of moles (B).

As it can be observed, most NADES mixtures reported in the database involve multiple hydrogen bonds acceptor units, where the average is 3.1 (insert in Figure 5A) but where the range spans between 0 and 18. This shows the complex role of some of the molecules were listed as HBA, including known complexing agents like zinc chloride [51]. On the other hand, the number of hydrogen bonds donated exhibits a slightly broader distribution, but spanning from 0 to 17 (Figure 5B); a value that is in line with the average number of moles of HBA and HBD used in the NADES (see Section 3.2). Also, the average hydrogen bonds donor units per NADES is 5.1, as represented in the blue dotted line box. These findings suggest that, on average, the formation of NADES require a total number of groups participating as hydrogens bond donor that is 64.5% higher than the total number of groups participating as hydrogens bond acceptor. This may provide insights into the versatility of NADES-analyte systems, as a higher number of hydrogen bond donors can engage in multiple hydrogen bond interactions with diverse analytes, supporting, for example, extraction procedures [7, 52].

3.4. Partition coefficient and molecular weight. A compound's ability to partition between two immiscible solvent phases (for example, n-octanol and water) is a well-established phenomenon. This value is characterized by a parameter known as the partition coefficient (P) or, for easier interpretation, logP. A high

logP value suggests that a compound displays hydrophobic behavior. Conversely, a low logP value implies hydrophilic behavior. In this context, the investigation of the logP of the compounds reported to form NADES system is crucial, as it contributes to the cumulative influence on the system's logP and, consequently, the final application of the eutectic mixture. Aiming to get further insights regarding the overall NADES's hydrophilicity or hydrophobicity, we analyzed the distribution of both the molecular weight and logP, for the individual components leading to the formation of NADES (Figure 7A and B).

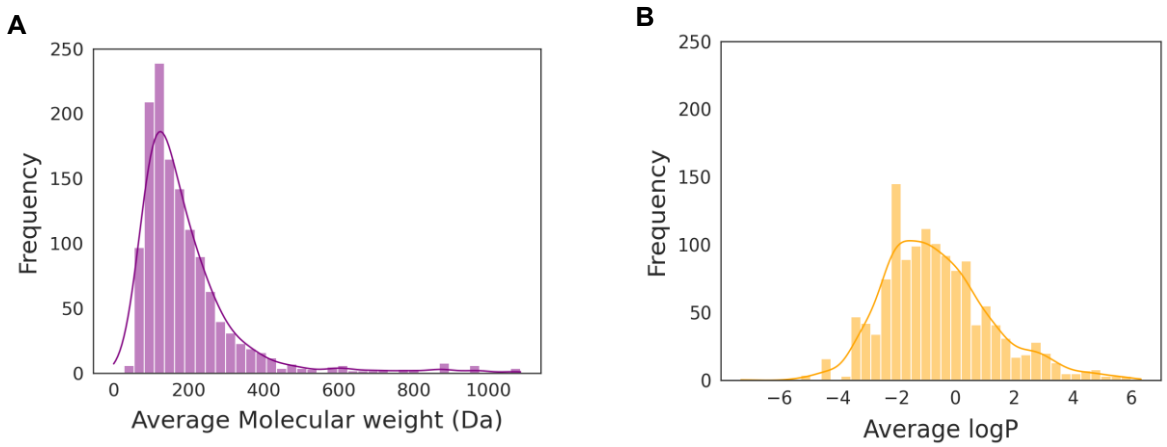


Figure 6: Frequency distribution of the molecular weight (A) and logP (B) of the components reported form NADES

As it can be observed in Figure 7A, most of the NADES reported in the database display a rather narrow distribution range in molecular weights (from 50 to 1000 Da) and a maximum at right below 200 Da (Figure 7A). In other words, the vast majority of the reported NADES have been designed with small molecules, enabling the alignment of these molecules with the formation of the corresponding hydrogen bonds [45].

In addition, it is important to note that the typical NADES's constituents feature logP values in the -7 to 6 range (Figure 7B, average logP = -0.6). This finding was somewhat surprising, since the most commonly reported NADES include hydrophilic components (Figure 3). Despite their initial impact [53], NADES synthetized with hydrophobic components clearly gained popularity after Osch *et al.* demonstrated the applicability of these solvents as water-immiscible extractants [54]. As expected, some studies indicate that the primary distinction between hydrophobic and hydrophilic NADES relies on the length of the aliphatic carbon chain of its constituents, making the hydrophilic moiety of the solvent's constituents less relevant than the hydrophobic one [54-56]. This distribution of values prompted the question to whether the

hydrophobicity of the selected components had a significant role on the formation of NADES. To answer this question, we calculated the average and standard deviation of the logP for each component, in each mixture listed in the database. This analysis showed that stable NADES are typically formed with small molecules that display similar characteristics, where the standard deviation calculated from the corresponding logP values is (for most cases) < 3 (Figure 7A).

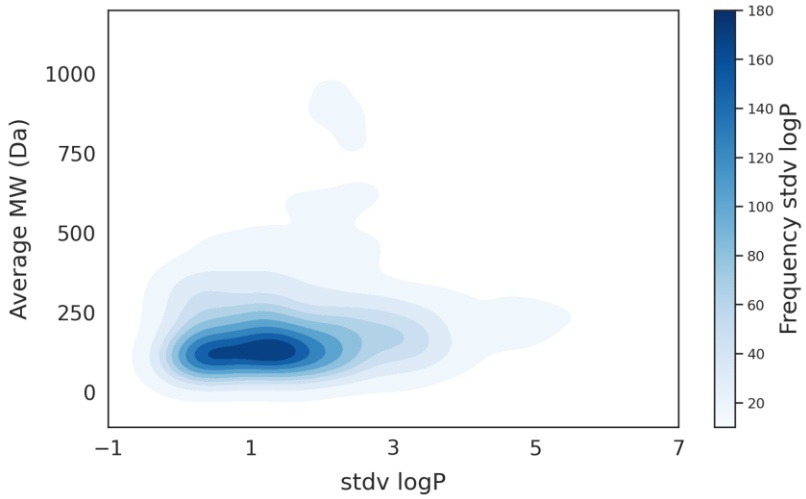


Figure 7: Heat map highlighting the distribution for the molecular weight and standard deviation of logP for the components leading to the formation of stable NADES.

This finding is somewhat reasonable, as it is intuitively simpler to mix components with similar characteristics, which would spontaneously lead to a single phase, even prior to heating/stirring. It is worth mentioning that while several authors have explored the possibility to use NADES as dispersants [57] or towards the formation of emulsions [58], this field seems to be relatively unexplored.

3.5. Water content. While some reports suggest that the addition of water does not affect the interaction of the main components in a NADES [32], others suggest that water has the potential to modulate the microstructure of DES and the resulting properties [25, 59, 60], potentially affecting the number hydrogen bonds as well as the strength of the interaction [61]. As it will be later discussed, the addition of water to some NADES could contribute to decreasing their overall viscosity but excessive additions could compete with the hydrogen bond network [62] and, consequently, affect the stability of these eutectic mixtures [59, 63]. Not surprisingly, even if components with different characteristics are used to form stable NADES, only

those formed with hydrophilic components (logP = -1.8 $\pm$ 0.6) can tolerate the addition of water (as a tertiary component). In these cases, mixtures containing up to 40% (mole ratio) are typically reported. While NADES containing higher amounts of water have been reported [60, 64], it possible that such NADES are maintained by other forces, leading to stable systems even if the integrity of the 3D network of hydrogen bonds is compromised [62, 65].

3.6. Density. Along with other rheologic properties, considering the density of NADES is critical for their rational use [66]. Typically, hydrophilic NADES have a density higher than that of water but ranging from 800 to 1600 $kg.m^{-3}$. Hydrophobic DES density offer an even wider range [66-68]. In both cases, increases in both temperature and water content typically lead to decreases in density [53, 69]. The former is ascribed to the increase in molecular movement and molar volume, while the latter is attributed to changes in NADES molecular packing. That said, our analysis shows that the structure of the components plays a determining factor on the density of the NADES. For example, the density of the NADES increases as the number of hydroxyl groups increases, supporting the notion that the strength of the hydrogen bond network is influenced by the amount and type of hydrogen bond donor present in the solvent [70-72]. In addition, Mohd Fuad *et al.* [53] reported that compounds with high molecular weight lead to NADES with higher densities, suggesting that this effect can be linked to the number of hydrogen bond donor/acceptor units. Although such trends are supported by specific systems [73, 74], the overall analysis of the database (as a function of the relevant chemical descriptors) only showed general decreases in density as the HBA/HBD ratio increases (Figure 8A and B, measured at 30 ^{o}C and 40 ^{o}C). While these trends do not appear to be a general rule applicable to all NADES, these findings are in agreement with several literature reports describing properties of specific formations [73, 75].

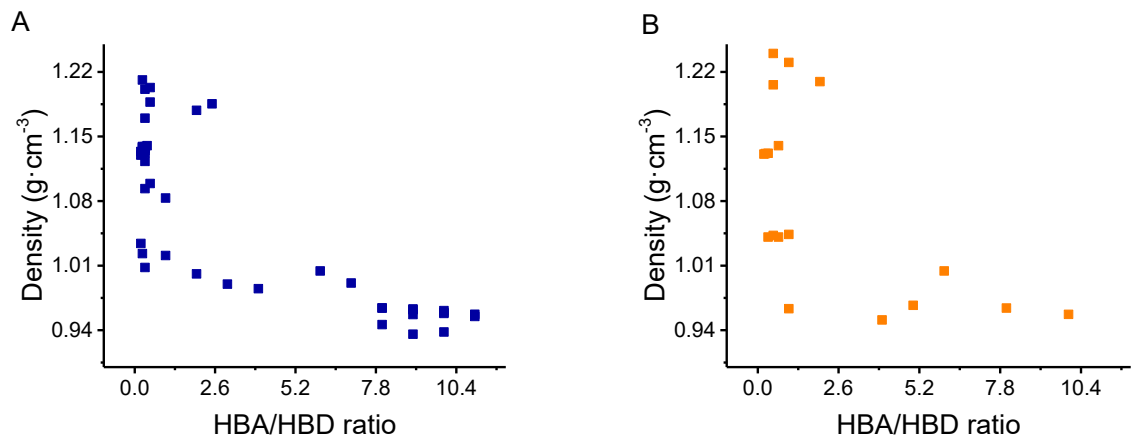


Figure 8: Dependence of density of NADES as a function of HBA/HBD ratio at 30°C (A) and 40°C (B).

3.7. Viscosity. Most reported NADES are highly viscous at room temperature, characteristic that is also attributed to the strong hydrogen bonding network among their components [59] and that represents the most pressing obstacle for their implementation in a wide variety of fields [9]. Aiming to control the viscosity of NADES, researchers have reported the use of hydrophobicity, water content, and temperature. For example, compared to choline based and hydrophobic NADES, sugar and metal salts-based NADES generally have higher viscosity [76]. As previously mentioned, increasing water content, often as third component in the NADES, decreases viscosity by weakening the hydrogen boding network while, ideally, maintaining overall structure. Indeed, the data included in the review published by Omar and Sadeghi [37] shows that NADES containing water in their composition displayed lower viscosities (average = 320 mPa·s) than binary NADES formulations (average = 1700 mPa·s). It is important to emphasize that, despite an in-depth examination of our database, temperature emerged as the only definitive variable showing a significant effect on viscosity, a fact that has been already reported by several authors [77-79].

4. CONCLUSIONS

The field of NADES represents a promising and growing topic for research and industry that is seeded with opportunities and questions. Aiming to contribute to the growing knowledge in this field, this manuscript presents a comprehensive analysis of trends and patterns in the NADES reported in the last decade. Out of this analysis, choline chloride emerged as the most common hydrogen bond acceptor; often paired with

glycerol, ethylene glycol, urea, levulinic acid, and glucose. According to the analysis also, the formation of NADES requires a slight excess of hydrogens bond donors over the total number of groups participating as hydrogens bond acceptor, challenging stoichiometric notions linked to hydrogen bonding [80]. Furthermore, our analysis highlighted the overwhelming contribution of small molecules (over polymer-based NADES [7]) and that the successful formation of NADES requires a careful selection of components and their compatibility (logP). While water can be used to modulate some of the properties (viscosity, density, etc.) of NADES, its addition is not risk-free, as it may destabilize the hydrogen bond network. All things considered, this study offers insights into general properties and characteristics of NADES reported, providing an example of how the integration of data analytics could help understanding general trends in the data in the chemical space. Optimistically, this analysis will allow researchers to address deep problems in NADES formation and select appropriately components for specific purposes, fostering advancements in utilizing NADES in new applications. However, and regardless of the volume of information available, it is important to acknowledge that there are still complexities and underexplored properties in these solvents (such as toxicity or long-term stability), that could represent promising targets for future studies.

5. COMPETING INTERESTS

The authors declare no competing interest

6. ACKNOWLEDGMENTS

Financial support for this project has been provided by the Department of Chemistry at Clemson University, the South Carolina Department of Agriculture ACRE Competitive Grant Program, and the NSF REU Program (CHE 2050042 & CHE-222737). Clemson University is also acknowledged for their generous allotment of computer time on the Palmetto Cluster.

7. REFERENCES

[1] S.M. Azcarate, R. Elia Dazat, J.M. Camiña, M.F. Silva, F.J.V. Gomez, NADES-modified voltammetric sensors and information fusion for detection of honey heat alteration, Food Control 140 (2022) 109144.

[2] B. Bradić, U. Novak, B. Likozar, Crustacean shell bio-refining to chitin by natural deep eutectic solvents, Green Process. Synth. 9 (2020) 13.

[3] C. Cannavacciuolo, S. Pagliari, J. Frigerio, C.M. Giustra, M. Labra, L. Campone, Natural Deep Eutectic Solvents (NADESs) Combined with Sustainable Extraction Techniques: A Review of the Green Chemistry Approach in Food Analysis, Foods 12 (2023) 56.

[4] D.C. de Andrade, S.A. Monteiro, J. Merib, A review on recent applications of deep eutectic solvents in microextraction techniques for the analysis of biological matrices, Advances in Sample Preparation 1 (2022) 100007.

[5] O. Długosz, Natural Deep Eutectic Solvents in the Synthesis of Inorganic Nanoparticles, Materials 16 (2023) 627.

[6] S. Emami, A. Shayanfar, Deep eutectic solvents for pharmaceutical formulation and drug delivery applications, Pharm Dev Technol 25 (2020) 779.

[7] F.J.V. Gomez, E. Vidal, C.E. Domini, G. Zanini, M.F. Silva, C.D. Garcia, Lab-on-a-bead: Polymeric natural deep eutectic solvents as a versatile platform for (bio)sensor design, J. Mol. Liq. 383 (2023) 122040.

[8] X. Liu, Y. Zhai, Z. Xu, Y. Zhu, Y. Zhou, Z. Wang, L. Liu, F. Liang, W. Ren, Y. Xie, C. Li, M. Xu, One-pot production of 5-methylfurfural (5-MF) and enhanced dewaterability of waste activated sludge by hydrothermal treatment with natural deep eutectic solvents (NADES): Experimental and theoretical studies, Chem. Eng. J. 464 (2023) 142575.

[9] Y. Liu, J.B. Friesen, J.B. McAlpine, D.C. Lankin, S.-N. Chen, G.F. Pauli, Natural Deep Eutectic Solvents: Properties, Applications, and Perspectives, J. Nat. Prod. 81 (2018) 679.

[10] Y. Liu, Y. Wu, J. Liu, W. Wang, Q. Yang, G. Yang, Deep eutectic solvents: Recent advances in fabrication approaches and pharmaceutical applications, Int. J. Pharm. 622 (2022) 121811.

[11] D. Rente, M. Cvjetko Bubalo, M. Panić, A. Paiva, B. Caprin, I. Radojčić Redovniković, A.R.C. Duarte, Review of deep eutectic systems from laboratory to industry, taking the application in the cosmetics industry as an example, J. Clean. Prod. 380 (2022) 135147.

[12] Y.H. Choi, J. van Spronsen, Y. Dai, M. Verberne, F. Hollmann, I.W.C.E. Arends, G.-J. Witkamp, R. Verpoorte, Are Natural Deep Eutectic Solvents the Missing Link in Understanding Cellular Metabolism and Physiology?, Plant Physiol. 156 (2011) 1701.

[13] A. García-Roldán, L. Piriou, P. Jauregi, Natural deep eutectic solvents as a green extraction of polyphenols from spent coffee ground with enhanced bioactivities, Front. Plant Sci. 13 (2023).

[14] Z. Usmani, M. Sharma, M. Tripathi, T. Lukk, Y. Karpichev, N. Gathergood, B.N. Singh, V.K. Thakur, M. Tabatabaei, V.K. Gupta, Biobased natural deep eutectic system as versatile solvents: Structure, interaction and advanced applications, Sci. Total Environ. 881 (2023) 163002.

[15] N.P.E. Hikmawanti, D. Ramadon, I. Jantan, A. Mun'im, Natural Deep Eutectic Solvents (NADES): Phytochemical Extraction Performance Enhancer for Pharmaceutical and Nutraceutical Product Development, Plants 10 (2021) 2091.

[16] J. Płotka-Wasylka, M. de la Guardia, V. Andruch, M. Vilková, Deep eutectic solvents vs ionic liquids: Similarities and differences, Microchem. J. 159 (2020) 105539.

[17] A.P. Abbott, K.J. Edler, A.J. Page, Deep eutectic solvents—The vital link between ionic liquids and ionic solutions, J. Chem. Phys. 155 (2021) 150401.

[18] L. Benvenutti, A.A.F. Zielinski, S.R.S. Ferreira, Which is the best food emerging solvent: IL, DES or NADES?, Trends Food Sci. 90 (2019) 133.

[19] N.P. Hikmawanti, D. Ramadon, I. Jantan, A. Mun'im, Plants, 2021.

[20] C.L. Boldrini, N. Manfredi, F.M. Perna, V. Capriati, A. Abbotto, Eco-Friendly Sugar-Based Natural Deep Eutectic Solvents as Effective Electrolyte Solutions for Dye-Sensitized Solar Cells, ChemElectroChem 7 (2020) 1707.

[21] M. Li, Y. Liu, F. Hu, H. Ren, E. Duan, Amino Acid-Based Natural Deep Eutectic Solvents for Extraction of Phenolic Compounds from Aqueous Environments, Processes 9 (2021) 1716.

[22] Y. Fan, H. Wu, D. Cai, T. Yang, L. Yang, Effective extraction of harmine by menthol/anise alcohol-based natural deep eutectic solvents, Sep. Purif. Technol. 250 (2020) 117211.

[23] C. Fan, T. Sebbah, Y. Liu, X. Cao, Terpenoid-capric acid based natural deep eutectic solvent: Insight into the nature of low viscosity, Clean. Eng. Technol. 3 (2021) 100116.

[24] M.d.l.Á. Fernández, J. Boiteux, M. Espino, F.J.V. Gomez, M.F. Silva, Natural deep eutectic solvents-mediated extractions: The way forward for sustainable analytical developments, Anal. Chim. Acta 1038 (2018) 1.

[25] S. Kaur, M. Kumari, H.K. Kashyap, Microstructure of Deep Eutectic Solvents: Current Understanding and Challenges, J. Phys. Chem. B 124 (2020) 10601.

[26] H. Palmelund, M.P. Andersson, C.J. Asgreen, B.J. Boyd, J. Rantanen, K. Löbmann, Tailor-made solvents for pharmaceutical use? Experimental and computational approach for determining solubility in deep eutectic solvents (DES), Int. J. Pharm.: X 1 (2019) 100034.

[27] C. Velez, O. Acevedo, Simulation of deep eutectic solvents: Progress to promises, Wiley Interdiscip. Rev. Comput. Mol. Sci. 12 (2022) e1598.

[28] K. Xin, F. Gallucci, M. van Sint Annaland, Development of Natural Hydrophobic Deep Eutectic Solvents for Precombustion CO2 Capture, ACS Sustain. Chem. Eng. 10 (2022) 15284.

[29] A. Kovács, E.C. Neyts, I. Cornet, M. Wijnants, P. Billen, Modeling the Physicochemical Properties of Natural Deep Eutectic Solvents, ChemSusChem 13 (2020) 3789.

[30] Z. Naseem, R.A. Shehzad, A. Ihsan, J. Iqbal, M. Zahid, A. Pervaiz, G. Sarwari, Theoretical investigation of supramolecular hydrogen-bonded choline chloride-based deep eutectic solvents using density functional theory, Chem. Phys. Lett. 769 (2021) 138427.

[31] V. Malaiyarasan, V. Vijayan Nithya, A. Ramalingam, S. Ramalingam, Density Functional Theory Study of the Molecular Interaction between Selective Phenolic Compounds and Glycerol-Based Deep Eutectic Solvents, ACS Agric. Sci. Technol. 3 (2023) 110.

[32] T. Di Pietro, L. Cesari, F. Mutelet, Influence of water on the conformations and interactions within two choline chloride-based deep eutectic solvents: a density functional theory investigation, Struct. Chem. (2023).

[33] T. Altamash, M.S. Nasser, Y. Elhamarnah, M. Magzoub, R. Ullah, B. Anaya, S. Aparicio, M. Atilhan, Gas Solubility and Rheological Behavior of Natural Deep Eutectic Solvents (NADES) via Combined Experimental and Molecular Simulation Techniques, ChemistrySelect 2 (2017) 7278.

[34] V.M. Nagulapati, H.M. Raza Ur Rehman, J. Haider, M. Abdul Qyyum, G.S. Choi, H. Lim, Hybrid machine learning-based model for solubilities prediction of various gases in deep eutectic solvent for rigorous process design of hydrogen purification, Sep. Purif. Technol. 298 (2022) 121651.

[35] M. Abdollahzadeh, M. Khosravi, B. Hajipour Khire Masjidi, A. Samimi Behbahan, A. Bagherzadeh, A. Shahkar, F. Tat Shahdost, Estimating the density of deep eutectic solvents applying supervised machine learning techniques, Sci. Rep. 12 (2022) 4954.

[36] L.B. Ayres, F.J.V. Gomez, M.F. Silva, J.R. Linton, C.D. Garcia, Predicting the Formation of NADES Using a Transformer-Based Model, Sci. Rep. (2024).

[37] K.A. Omar, R. Sadeghi, Database of deep eutectic solvents and their physical properties: A review, J. Mol. Liq. 384 (2023) 121899.

[38] S.M. Azcarate, R. Ríos-Reina, J.M. Amigo, H.C. Goicoechea, Data handling in data fusion: Methodologies and applications, TrAC, Trends Anal. Chem. 143 (2021) 116355.

[39] D.O. Abranches, J.A.P. Coutinho, Everything You Wanted to Know about Deep Eutectic Solvents but Were Afraid to Be Told, Annu. Rev. Chem. Biomol. 14 (2023) 141.

[40] Y. Dai, J. van Spronsen, G.-J. Witkamp, R. Verpoorte, Y.H. Choi, Natural deep eutectic solvents as new potential media for green technology, Anal. Chim. Acta 766 (2013) 61.

[41] R. Amoroso, F. Hollmann, C. Maccallini, Choline Chloride-Based DES as Solvents/Catalysts/Chemical Donors in Pharmaceutical Synthesis, Molecules 26 (2021) 6286.

[42] M.L. Picchio, D. Minudri, D. Mantione, M. Criado-Gonzalez, G. Guzmán-González, R. Schmarsow, A.J. Müller, L.C. Tomé, R.J. Minari, D. Mecerreyes, Natural Deep Eutectic Solvents Based on Choline Chloride and Phenolic Compounds as Efficient Bioadhesives and Corrosion Protectors, ACS Sustain. Chem. Eng. 10 (2022) 8135.

[43] R.E. Dazat, E. Vidal, A.S. Lorenzetti, C.D. García, C. Domini, M.F. Silva, F.J.V. Gomez, On-Site Preparation of Natural Deep Eutectic Solvents Using Solar Energy, ChemistrySelect 7 (2022) e202104362.

[44] L. Gontrani, N.V. Plechkova, M. Bonomo, In-Depth Physico-Chemical and Structural Investigation of a Dicarboxylic Acid/Choline Chloride Natural Deep Eutectic Solvent (NADES): A Spotlight on the Importance of a Rigorous Preparation Procedure, ACS Sustain. Chem. Eng. 7 (2019) 12536.

[45] P.L. Pisano, M. Espino, M.d.l.Á. Fernández, M.F. Silva, A.C. Olivieri, Structural analysis of natural deep eutectic solvents. Theoretical and experimental study, Microchem. J. 143 (2018) 252.

[46] M. Espino, M. de los Ángeles Fernández, F.J.V. Gomez, M.F. Silva, Natural designer solvents for greening analytical chemistry, TrAC, Trends Anal. Chem. 76 (2016) 126.

[47] L. Al Fuhaid, M.F. Nava-Ocampo, S.S. Bucs, R. Verpoorte, Y.H. Choi, G.-J. Witkamp, A.S.F. Farinha, Crystallization and time-dependent changes in betaine-urea-water natural deep eutectic solvents, J. Mol. Liq. 387 (2023) 122718.

[48] M.F. Nava-Ocampo, L. Al Fuhaid, A. Santana, S.S. Bucs, R. Verpoorte, Y. Hae Choi, G.J. Witkamp, J.S. Vrouwenvelder, A.S.F. Farinha, Structural properties and stability of the Betaine-Urea natural deep eutectic solvent, J. Mol. Liq. 343 (2021) 117655.

[49] A. Pandey, Bhawna, D. Dhingra, S. Pandey, Hydrogen Bond Donor/Acceptor Cosolvent-Modified Choline Chloride-Based Deep Eutectic Solvents, J. Phys. Chem. B 121 (2017) 4202.

[50] R. Yusof, E. Abdulmalek, K. Sirat, M.B. Rahman, Molecules, 2014, p. 8011.

[51] F.S. Ghareh Bagh, K. Shahbaz, F.S. Mjalli, M.A. Hashim, I.M. AlNashef, Zinc (II) chloride-based deep eutectic solvents for application as electrolytes: Preparation and characterization, J. Mol. Liq. 204 (2015) 76.

[52] D. Rente, A. Paiva, A.R. Duarte, The Role of Hydrogen Bond Donor on the Extraction of Phenolic Compounds from Natural Matrices Using Deep Eutectic Systems, Molecules 26 (2021).

[53] F. Mohd Fuad, M. Mohd Nadzir, A. Harun@Kamaruddin, Hydrophilic natural deep eutectic solvent : A review on physicochemical properties and extractability of bioactive compounds, J. Mol. Liq. 339 (2021) 116923.

[54] D.J.G.P. van Osch, L.F. Zubeir, A. van den Bruinhorst, M.A.A. Rocha, M.C. Kroon, Hydrophobic deep eutectic solvents as water-immiscible extractants, Green Chem. 17 (2015) 4518.

[55] M. Devi, R. Moral, S. Thakuria, A. Mitra, S. Paul, Hydrophobic Deep Eutectic Solvents as Greener Substitutes for Conventional Extraction Media: Examples and Techniques, ACS Omega 8 (2023) 9702.

[56] C. Florindo, L.C. Branco, I.M. Marrucho, Quest for Green-Solvent Design: From Hydrophilic to Hydrophobic (Deep) Eutectic Solvents, ChemSusChem 12 (2019) 1549.

[57] L. Carbonell-Rozas, R. Canales, F.J. Lara, A.M. García-Campaña, M.F. Silva, A natural deep eutectic solvent as a novel dispersive solvent in dispersive liquid-liquid microextraction based on solidification of floating organic droplet for the determination of pesticide residues, Anal. Bioanal. Chem. 413 (2021) 6413.

[58] S. Bi, H. Liu, H. Lin, P. Wang, Integration of natural deep-eutectic solvent and surfactant for efficient synthesis of chiral aromatic alcohol mediated by Cyberlindnera saturnus whole cells, Biochem. Eng. J. 172 (2021) 108053.

[59] Y. Dai, G.-J. Witkamp, R. Verpoorte, Y.H. Choi, Tailoring properties of natural deep eutectic solvents with water to facilitate their applications, Food Chem. 187 (2015) 14.

[60] M. Vilková, J. Płotka-Wasylka, V. Andruch, The role of water in deep eutectic solvent-base extraction, J. Mol. Liq. 304 (2020) 112747.

[61] X. Wang, B. Liu, H. Yang, J. Tian, Properties of binary mixtures of a novel natural deep eutectic solvent (glycolic acid + xylitol) and water at several temperatures, Fluid Ph. Equilibria 556 (2022) 113390.

[62] D. Herschlag, M.M. Pinney, Hydrogen Bonds: Simple after All?, Biochem. 57 (2018) 3338.

[63] T. Zhekenov, N. Toksanbayev, Z. Kazakbayeva, D. Shah, F.S. Mjalli, Formation of type III Deep Eutectic Solvents and effect of water on their intermolecular interactions, Fluid Ph. Equilibria 441 (2017) 43.

[64] R. Craveiro, V.I.B. Castro, M.T. Viciosa, M. Dionísio, R.L. Reis, A.R.C. Duarte, A. Paiva, Influence of natural deep eutectic systems in water thermal behavior and their applications in cryopreservation, J. Mol. Liq. 329 (2021) 115533.

[65] S.C.C. van der Lubbe, C. Fonseca Guerra, The Nature of Hydrogen Bonds: A Delineation of the Role of Different Energy Components on Hydrogen Bond Strengths and Lengths, Chem. Asian J. 14 (2019) 2760.

[66] L.K. Savi, D. Carpiné, N. Waszczynskyj, R.H. Ribani, C.W.I. Haminiuk, Influence of temperature, water content and type of organic acid on the formation, stability and properties of functional natural deep eutectic solvents, Fluid Ph. Equilibria 488 (2019) 40.

[67] T. El Achkar, H. Greige-Gerges, S. Fourmentin, Basics and properties of deep eutectic solvents: a review, Environ. Chem. Lett. 19 (2021) 3397.

[68] A.K. Halder, R. Haghbakhsh, I.V. Voroshylova, A.R.C. Duarte, M.N.D.S. Cordeiro, Density of Deep Eutectic Solvents: The Path Forward Cheminformatics-Driven Reliable Predictions for Mixtures, Molecules 26 (2021) 5779.

[69] N.F. Gajardo-Parra, L. Meneses, A.R.C. Duarte, A. Paiva, C. Held, Assessing the Influence of Betaine-Based Natural Deep Eutectic Systems on Horseradish Peroxidase, ACS Sustain. Chem. Eng. 10 (2022) 12873.

[70] G. García, S. Aparicio, R. Ullah, M. Atilhan, Deep Eutectic Solvents: Physicochemical Properties and Gas Separation Applications, Energy Fuels 29 (2015) 2616.

[71] J. Hoppe, R. Drozd, E. Byzia, M. Smiglak, Deep eutectic solvents based on choline cation - Physicochemical properties and influence on enzymatic reaction with β-galactosidase, Int. J. Biol. Macromol. 136 (2019) 296.

[72] A. Basaiahgari, S. Panda, R.L. Gardas, Effect of Ethylene, Diethylene, and Triethylene Glycols and Glycerol on the Physicochemical Properties and Phase Behavior of Benzyltrimethyl and Benzyltributylammonium Chloride Based Deep Eutectic Solvents at 283.15–343.15 K, J. Chem. Eng. Data 63 (2018) 2613.

[73] B.B. Hansen, S. Spittle, B. Chen, D. Poe, Y. Zhang, J.M. Klein, A. Horton, L. Adhikari, T. Zelovich, B.W. Doherty, B. Gurkan, E.J. Maginn, A. Ragauskas, M. Dadmun, T.A. Zawodzinski, G.A. Baker, M.E. Tuckerman, R.F. Savinell, J.R. Sangoro, Deep Eutectic Solvents: A Review of Fundamentals and Applications, Chem. Rev. 121 (2021) 1232.

[74] C.C. Fernandes, A. Paiva, R. Haghbakhsh, A. Rita C. Duarte, Is it possible to correlate various physicochemical properties of Natural Deep eutectic systems in order to predict their behaviours as solvents?, J. Mol. Liq. 384 (2023) 122280.

[75] M.H. Shafie, R. Yusof, C.-Y. Gan, Synthesis of citric acid monohydrate-choline chloride based deep eutectic solvents (DES) and characterization of their physicochemical properties, J. Mol. Liq. 288 (2019) 111081.

[76] C. Fanali, V. Gallo, S. Della Posta, L.A.-O. Dugo, L.A.-O. Mazzeo, M.A.-O. Cocchi, V.A.-O. Piemonte, L.A.-O. De Gara, Choline Chloride-Lactic Acid-Based NADES As an Extraction Medium in a Response Surface Methodology-Optimized Method for the Extraction of Phenolic Compounds from Hazelnut Skin. LID - 10.3390/molecules26092652 [doi] LID - 2652.

[77] A. Bakhtyari, R. Haghbakhsh, A.R.C. Duarte, S. Raeissi, A simple model for the viscosities of deep eutectic solvents, Fluid Ph. Equilibria 521 (2020) 112662.

[78] R. Craveiro, I. Aroso, V. Flammia, T. Carvalho, M.T. Viciosa, M. Dionísio, S. Barreiros, R.L. Reis, A.R.C. Duarte, A. Paiva, Properties and thermal behavior of natural deep eutectic solvents, J. Mol. Liq. 215 (2016) 534.

[79] L.K. Savi, M.C.G.C. Dias, D. Carpine, N. Waszczynskyj, R.H. Ribani, C.W.I. Haminiuk, Natural deep eutectic solvents (NADES) based on citric acid and sucrose as a potential green technology: a

comprehensive study of water inclusion and its effect on thermal, physical and rheological properties, Int. J. Food Sci. Technol. 54 (2019) 898.

[80] I.S. Ryu, X. Liu, Y. Jin, J. Sun, Y.J. Lee, Stoichiometric analysis of competing intermolecular hydrogen bonds using infrared spectroscopy, RSC Adv. 8 (2018) 23481.