Computer simulation applied to structural analysis and experimental applications of natural deep eutectic solvents



Otávio Aguiar Souza^a, Daniel Rinaldo^{a,b}, Caio M. Porto^d, Júlio R. Sambrano^c, Nelson H. Morgon^d, and Aguinaldo R. de Souza^b

^aUNESP—São Paulo State University, Chemistry Graduate Program, Institute of Chemistry, Araraquara, São Paulo, Brazil, ^bUNESP—São Paulo State University, Chemistry Department, School of Sciences, Bauru, São Paulo, Brazil, ^cUNESP—São Paulo State University, Molecular and Simulation Group, Mathematics Department, School of Sciences, Bauru, São Paulo, Brazil, ^dUNICAMP—Campinas State University, Physics and Chemistry Department, Institute of Chemistry, Campinas, São Paulo, Brazil

1. Introduction

Green Technology, one of the main areas of interest in chemistry in current days, focuses on preserving the environment and minimizing negative anthropic impacts on it. The reduction of the use of hazardous media and the maximization of the use of non-hazardous ones, as well as the employment of new eco-friendly techniques and the development of new green alternative solvents, is possibly the most active area in the green chemistry context [1, 2].

Solvents are often responsible for major amounts of wastes in syntheses and processes; on the other hand, they are almost indispensable, as they play key roles in dissolution, mass and heat transfer, purification, separation, and other operations [2, 3]. Therefore, developing environmentally friendly solvents as substitutes for non-green-ones is simultaneously a major challenge and a prioritized target [2, 4, 5]. Coherently with this, one of the main priorities of the EU environmental policy and legislation for the 2010–50 period is to significantly reduce the use of volatile organic compounds, or VOCs, (because these chemicals present volatility, flammability, and often also high toxicity), and/or solvents of diverse origins, replacing them with greener ones and/or ones of renewable origin, which simultaneously also fits economic and technological goals [3, 6, 7].

Over decades, ionic liquids (ILs) have gained increasing attention from the scientific community as alternative solvents [2, 8]. They can be formed through the association of a coordinating anion (e.g., a pyridinium or imidazolium halide) with a complexing agent (e.g., an acid), inducing charge delocalization and promoting the

Green Chemistry and Computational Chemistry. https://doi.org/10.1016/B978-0-12-819879-7.00043-X Copyright © 2022 Elsevier Inc. All rights reserved.

decrease of the interaction with the positive ion [9, 10]. These compounds have been reported in the literature since 1914 [11, 12]. However, ILs usually present low biocompatibility and biodegradability and, therefore, low sustainability [8]. Between 2002 and 2003, this scenario changed when Abbott and co-workers [13] introduced the deep eutectic solvents (DES). Their paper reported a mixture containing solid choline chloride and urea, both of which have high melting points when separated. These mixtures form a eutectic system [13] (i.e., a system that usually melts at a much lower temperature in comparison to the melting points of its starting components). The supramolecular structure of a DES is kept together by a hydrogen bonding network and/or van der Waals interactions. These interactions force the DES to remain liquid in a wide range of temperatures. The ability to establish combinations of hydrogen bond donor-acceptor interactions (HBD-HBA interactions) allows the tailoring of the physical properties and of the chemical and/or phase behaviours of these compounds, making them suitable for being employed as solvents [2, 14]. When the starting materials are abundant in cellular media, as it is the case of sugars, amino acids, organic acids, and choline derivatives, these solvents are termed natural deep eutectic solvents (NADES) [2]. NADES have emerged in the last decade and, similarly to DES, appear as valuable and promising green alternative media to widely employed harmful solvents [2, 15].

Considering the potentialities of this relatively new class of solvents for the feasibility of more sustainable chemical processes, this chapter provides detailed descriptions of the properties of NADES from both an experimental and a theoretical point of view. Examples of computational results from the study of selected NADES structures are presented, showing that quantum chemical calculations can be a powerful tool to improve the knowledge about the structure of these solvents and how their properties can be better tailored for a wide range of applications in academic and industrial contexts.

2. NADES: From discovery to current days

2.1 The discovery of NADES and their properties

The existence of NADES was first reported by Choi et al. [11]. Their pioneer work emphasizes that these fluids are formed by the combination of highly bio-renewable and bioavailable primary metabolites (e.g., organic acids, choline derivatives, sugars, amino acids), being nature-engineered and an alternative medium to water and lipids in the cells of some living organisms, including plants, mammalians, and microbes, and playing a key role in biochemical and physiological functions [11]. On the basis of relevant experimental evidence (e.g., the ¹H–¹H-nuclear Overhauser enhancement spectroscopy spectrum of a mixture formed by sucrose and malic acid, or tests that proved the higher solubility of rutin in some synthetized choline chloride-based NADES in comparison to water, or the enzymatic activity in NADES) or previous literature data, the authors [11] postulated that the presence of NADES in cells would be responsible for several biological processes, such as biosynthesis and storage of

macromolecules and/or water-insoluble metabolites, mostly in aqueous intracellular medium, as well as enzymatic activity and stability, germination, and defence or survival of some organisms in extreme conditions like excessive cold or drought [11]. Some of these postulates have been confirmed experimentally [1, 16–18]; thus, NADES are promising both within cellular biochemistry studies, where they can enable better understanding of certain biological mechanisms or pathways, and for their applications as green solvents [9].

In fact, NADES show desirable properties as solvents: adjustable viscosity, negligible volatility, higher capacity to dissolve several less polar compounds in comparison to conventional solvents, the ability to remain in the liquid phase at temperatures below 0 °C, reduced or null toxicity, biocompatibility, and low cost [1, 2, 6, 11, 19, 20]. Therefore, they can be viewed as a promising sustainable alternative.

A basic search performed on March 30, 2020, on ISI Web of Science (Clarivate Analytics) with the keywords 'natural deep eutectic solvents' returned 458 results. The database revealed more frequent publication of scientific documents regarding NADES in the 2018–19 period. The scientific production responding to this term pertains mostly to chemistry (multidisciplinary), chemical engineering, analytical chemistry, and food, science and technology; the countries with greater publication rates on this topic were China (25.55%), Spain (6.99%), the United States (6.77%), and India (ca. 5.9%). However, mixtures that can be classified as NADES often appear in literature with alternative denominations (keywords), which can hinder the popularization of the term in the scientific community, and its standardization (which would, for example, be convenient for bibliographic searches in specific databases), thus also hampering the applications of NADES, the overall knowledge about their advantages and, therefore, their consolidation as green solvents.

2.2 The consolidation of the 'NADES' term in the literature

Since these smart solvents represent a growing and relatively new research topic and their definition still remain a novelty, confusing or non-consistent information about them may be found in the literature, and this phenomenon is recognized by some authors [2, 9]. Different terms such as ionic liquids (IL), deep eutectic solvents (DES), and low-transition temperature mixtures (LTTMs) happen to be used indiscriminately (and sometimes incorrectly) to refer to NADES, most probably because all these types of solvents can share a theoretical common mechanism of formation (e.g., being formed by the combination of primary components) and similar physicochemical properties (e.g., low transition temperature, negligible or no volatility, and low vapour pressure) [9]. This confusion may be partially understandable since the NADES term is newer than the IL and DES ones: ILs and DES were introduced in the literature in 1914 [11, 12] and 2002/2003 [13], respectively. Also, there is a relationship between scientometric factors such as impact factor, number of citations of a given manuscript, or the career of the authors of the pioneer work on a particular solvent in the scientific literature, and the consolidation of the term among the scientific community.

Until 2011, only the IL and DES terms were available for denoting and classifying NADES, and in various works in the literature, both before and after 2011, they have been denoted with these alternative names [9, 14, 21, 22]. In view of some of their properties, they could actually fit in one or more of these alternative classes; furthermore, delimitating the boundaries among some of these classes of solvents is not always a trivial or even feasible task (e.g., for DES and NADES), and common properties among them lead some authors to classify IL, DES, and NADES as subfamilies of LTTMs. However, this confusion may become problematic in certain contexts, as some properties relevant to the possible applications of these solvents are distinct; examples are the reactivity, cost, and sustainable character of ILs in comparison to (NA)DES [8, 9].

2.3 Syntheses and main applications of NADES

According to Dai and co-workers [1], Espino and co-workers [2], and Gomez and co-workers [23], there are four methods for preparing NADES from the relevant starting compounds, employing distinct types of irradiation, agitation and/or physical phenomena to obtain a homogeneous solution: heating and stirring, evaporating, freeze-drying, and microwave preparation. The physicochemical properties of the prepared NADES are functions of their viscosity, conductivity, density, and polarity. The (NA)DES composition flexibility has made these mixtures a promising tool in many areas and for many applications, including electrochemistry [24], nanotechnology [25], and pharmacology [26].

One of the main applications of these mixtures is as green extraction media [19, 20]. Although this greenness can be questionable if the NADES-mediated extraction is followed by time- and energy-consuming or hazardous purification steps, extensive compounds' isolation or extractives' analysis [27], the literature presents at least one article in which NADES are employed as green extraction media and the analysis of the NADES-extracted compounds by liquid chromatography also employs green solvents as mobile phases [28]. In summary, NADES components can be prepared to be target-specific in many applications [29].

Theoretical studies applied to (NA)DES: How computational simulations can be useful to elucidate their potentialities

3.1 Roles and potentialities of computational studies

In recent years, many experimental and computer simulation studies have been carried out to understand the structure of NADES at the submicroscopic level and also with the objective of comprehending the intermolecular interactions responsible for their formation [30]. This section highlights how these studies can contribute to the consolidation of these solvents as objects of interest in the academia and industry. Singh and Singh [31] studied the phase diagram of the simple eutectic mixture of o-nitroaniline and α -naphtol. Results from the thermodynamic functions and the linear velocity of solidification demonstrated that the eutectic mixture is a non-ideal one. Ab initio computational simulations via electronic structure methods showed that the mixture is organized by stacking and side-by-side interactions and by the possibility of the formation of strong hydrogen bonds [31]. Similar study-perspectives can be explored or extrapolated for research involving (NA)DES.

Pisano and co-workers [29] performed a theoretical and experimental study on NADES formed by lactic acid-glucose, citric acid-fructose, and citric acid-glucose. The intermolecular interactions between the NADES components of the mixture were confirmed by the presence of multiple nuclear Overhauser effects (NOE) upon analysis of the ¹H NMR spectra, and after dilutions, the spatial proximity between the hydrogen atoms of the different NADES constituents were confirmed. Following the experimental results, a simplified computer simulation model of the same NADES reproduced the spatial proximity between the components of the mixture and lead to the understanding of the intermolecular interactions by revealing two complementary hydrogen bonds between the NADES components [29].

By employing the COSMO-RS methodology [32], Jeliński and co-workers [26] identified possible NADES having the ability to strongly solvate the rutin molecule, which makes it possible to screen for the most effective mixture to solvate rutin. This approach made use of the observed linear relationships between the data obtained experimentally and the activity coefficients values computed in the infinite dilution approximation. This strategy can be applied to model many multi-components systems, including NADES that have not yet been studied experimentally. The highest solubility of rutin was obtained using carboxylic acids whose chain contains two methylene groups and two amino groups, with the latter promoting enhanced acidity of the carboxylic acid. This leads to the dissociation of the amino acid component or to the formation of strongly basic centres on the carboxylic acid chain, thus promoting direct intermolecular interactions with the rutin molecule.

The rationalization of the melting temperature of NADES from density functional theory (DFT) results was presented by Garcia and co-workers [30], in combination with a topological analysis of the electronic density at the molecular level. The results showed a direct relationship between the melting temperature and the hydrogen bond network of NADES. They also showed that low electronic density at the cage critical points leads to low melting points. Thus, they showed that DFT computer simulation is a very useful approach for the rationalization and prediction of the macroscopic properties of NADES.

The atoms in molecules (AIM) methodology [33] has demonstrated its applicability in the determination of intermolecular interactions. According to this theory, there are four types of critical points suitable to the study of NADES: atomic critical points (ACP), bond critical points (BCP), ring critical points (RCP), and cage critical points (CCP). The analysis of the CCP allows studying the hydrogen bond networks as a whole, without the need to analyse each hydrogen bond individually. These features of AIM make it very suitable for the study of NADES systems that contain a large number of molecules and hydrogen bonds connections among them.

However, although studies as the aforementioned ones exist, the literature still lacks more research that use computer simulations simultaneously coupled with experimental investigation to more thoroughly explain some properties of NADES directly related to their applications. For example, regarding their high ability to dissolve biological macromolecules-the property which prompts their major application as greener extraction media—some studies investigate it only from a computational and theoretical perspective, others only from an experimental one; the latter simply hypothesize that the high solubility of some compounds—including macromolecules—is related to more effective interactions between these compounds and the supramolecular network of NADES, without any computer simulation to corroborate these affirmations. Coupling computer simulations and experimental studies offers the possibility to more accurately investigate both the NADES structure and the processes that they can mediate, thus opening global perspectives for vast applications of these emerging solvents in academic and industry contexts, which can include a more coherent use for green (analytical) chemistry applications. Furthermore, a better understanding of their structure is useful for the standardization of the use of the 'NADES' term in the literature, preventing misdefinitions or incorrect classifications.

The next section presents an example aimed at highlighting the perspectives of the application of coupled theoretical and experimental studies to better understand the potentialities of NADES as green and efficient solvents. The example uses a quantum chemical approach, with the density functional theory (DFT) level, to unravel the structure of NADES composed of the glucose sugar and the proline amino acid.

3.2 Structural study of selected NADES employing computational methodologies coupled with experimental results

It is already known, and it is increasingly more evident, that the synergy between theory and experiment is an essential condition for scientific development. In particular, quantum mechanical computational simulations can provide invaluable support for experimental data. Most theoretical methods render promising results, including the consideration of correlation energy and the addition of the self-consistent effect of a polarizable continuum medium (SCRF) mimicking the solvent of interest. Therefore, experimental research and complementary theoretical studies can lead to a deep understanding of the molecular level of chemical events.

In the example considered here, the molecular modelling of the NADES system initiated with the search for the most stable geometries of glucose and proline in the gas phase and, subsequently, in the presence of water solvent. The most stable conformations were optimized using the B3LYP [34] exchange correlation functional coupled with the all-electron 6-31 + G(d,p) basis set. This choice is reasonable for a first-order approach to a theoretical exploration of NADES. All the calculations were performed using the Gaussian 16 software [35].

It is important to emphasize that better practices in DFT simulations require the selection of an exchange-correlation functional, and it is well-known that lots of functionals have already been developed. Some of them can describe only the structural or

286

the electronic parameters with accuracy, but not always at the same time, which may lead to inaccurate evaluation of certain properties. An example is the case of the generalized approximation (GGA) and local density approximation (LDA), which, like some other functionals, generally overestimate the energy difference between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO). Therefore, the choice of the functional has a fundamental role for a realistic description of the properties of organic and inorganic molecular systems in DFT simulations.

The molecules' vibrational harmonic frequencies were calculated on the optimized geometries to confirm their minimum-energy nature. The self-consistent reaction field method (SCRF) was employed to simulate the solvent effects. In the SCRF model, a molecule in solution is enveloped in a cavity surrounded by a continuum with a dielectric constant (ε) to simulate the medium. In this study, the aqueous medium ($\varepsilon = 78.4$) was selected.

The non-covalent interactions (NCI) analysis [36] was performed using the NCIPLOT [37] software. In this analysis, the electron densities and reduced density gradients are investigated for density critical points that are absent when there is no interaction. The sign of the electron density Hessian eigenvalue (λ) is used to differentiate the types of interactions. For strong attractive interactions, as hydrogen bonds, λ is negative, and for repulsive interactions λ is positive. For weak attractive interactions, λ is close to zero.

Figs. 1 and 2 show the most stable conformers of the glucose and proline molecules; Fig. 3 shows their molecular surfaces with the charge distributions, and the dipole moment vectors, whose magnitudes are 4.11 and 1.82 Debye, respectively.

Table 1 reports the Mulliken charges on the atoms of the glucose and proline molecules. The negative charges are located on the C3, C5, O11, O12, O14, O16, O18, C20, and O23 atoms for glucose and on the N1, C2, C6, C7, O14, and O16 atoms for proline. On the other hand, the positive charges with a value greater than 0.30 a.u. are located on the C1, C2, H13, H15, H17, H19, and H24 atoms of glucose and the C9, H17 atoms of proline.

The analysis of the Mulliken charges on the atoms of glucose and proline suggests that the atoms of the COOH group of proline and the atoms of the OH groups on



Fig. 1 Most stable conformer and atom numbering of glucose. The conformer has the chair conformation.



Fig. 2 Most stable conformer and atom numbering of proline.



Fig. 3 Molecular surface, charge distribution and dipole moment vector of the lowest energy conformer of glucose (A) and of proline (B).

	Glucose	Proline		
Glucose				
Atom	Charge on the atom (a.u.)	Atom	Charge on the atom (a.u.)	
C1	0.27	N1	-0.34	
C2	0.30	C2	-0.17	
C3	-0.22	C3	-0.34	
C4	0.06	H4	0.13	
C5	-0.03	H5	0.14	
H6	0.13	C6	-0.30	
H7	0.17	C7	-0.09	
H8	0.16	H8	0.16	
H9	0.14	C9	0.42	
H10	0.15	H10	0.14	

Table 1 Mulliken charges (a.u.) on the atoms of glucose and proline. DFT/B3LYP/6-31 + G(d,p) results.

Glucose		Proline		
Atom	Charge on the atom (a.u.)	Atom	Charge on the atom (a.u.)	
011	-0.32	H11	0.16	
O12	-0.53	H12	0.15	
H13	0.36	H13	0.16	
O14	-0.49	014	-0.47	
H15	0.36	H15	0.29	
016	-0.56	016	-0.42	
H17	0.37	H17	0.37	
O18	-0.55			
H19	0.37			
C20	-0.20			
H21	0.15			
H22	0.14			
O23	-0.59			
H24	0.37			

Table 1 Continued

glucose are the most suitable for the formation of intermolecular hydrogen bonds (H-bonds) between the two molecules. Corresponding complexes were considered, investigating the characteristics of their hydrogen bonds, as well as their dipole moment, their molecular surface and charge distribution, and the interaction energies between the constituting molecules, in order to obtain more information about the most probable structural arrangements of glucose-proline NADES and about their properties. The interaction energy among the molecules forming a complex was evaluated, at the same level of theory and basis sets, through a counterpoise calculation incorporating the correction to the basis set superposition error [38].

The simulation was initially performed with 1:1 stoichiometry of glucose and proline, with the aim of identifying the most stable 1:1 complexes that the two molecules can form. Fig. 4 shows the models of the five optimized systems obtained, along with their molecular surfaces and charge distribution, and their dipole moment vectors. The systems are denoted by acronyms of the GPn type, where G denotes the glucose molecule, P denotes the proline molecule, and n indicates the position in the glucose molecule to which the proline molecule is attached, according to the scheme shown in Fig. 5; when the proline molecule H-bonds to two consecutive positions of the glucose molecule, their two numbers appear in place of n. Table 2 reports the length and the angle of the H-bonds between the two molecules, the dipole moments of the complexes, and the interaction energies between the two molecules. In the following analysis, as well as in the tables, the H-bonds are denoted utilizing the atom numbering of glucose shown in Fig. 1 and the atom numbering of proline shown in Fig. 2, for the sake of clarity, with the indication of the molecule in parentheses.



Fig. 4 Optimized geometries of the modeled complexes of glucose and proline with 1:1 stoichiometry.



Fig. 5 Numbering of the possible positions in the glucose molecule to which the proline molecule can attach via hydrogen bonds, utilized in the acronyms denoting their complexes. Number 1 represents the OH of the $-CH_2OH$ group, and the other positions represent the other OH groups. The O heteroatom is not numbered.

Two H-bonds are formed between the two molecules in all the calculated complexes, respectively, with H17 of proline as donor and with O14 of proline as acceptor. In GP1 and GP2, the proline molecule attaches to only one OH group of the glucose molecule, whereas in GP23, GP34, and GP45, it attaches to two consecutive OH groups. The two H-bonds close a six-member ring in the former case and a ninemember ring in the latter case. The lengths and the bond angles of the two H-bonds in the same complex are significantly different, with shorter length and greater linearity pertaining to the H-bonds in which H17(P) is the donor, except for GP34.

The magnitude of the interaction energy between the two molecules is considerably greater when the proline molecule attaches to two different OHs of the glucose molecule. This suggests non-negligible influence by geometry factors, or forms of interaction related to them, because the lengths of the two H-bonds in the two cases do not differ sufficiently to account for the large interaction-energy difference the interaction energy averaging 8.94 kcal/mol when proline attaches to only one site of glucose and 14.15 kcal/mol when it attaches to two sites.

	Length o	f hydrogen b	ond		
Model	Hydrogen bond considered	Length (Å)	Angle (°)	Dipole moment (Debye)	Complexation energy (corrected for BSSE) (kcal/mol)
GP1	H17 (P)···	1.764	158.76	2.71	-9.51
	O23 (G)	2.031	132.19		
	H24 (G)…				
	O14 (P)				
GP2	H17 (P)···	1.793	158.76	1.48	-8.37
	O12 (G)	2.107	127.06		
	H13 (G)…				
	O14 (P)				
GP23	H17 (P)···	1.773	166.20	2.77	-14.58
	O14 (G)	1.964	155.65		
	H13 (G)…				
	O14 (P)				
GP34	H15 (G)…	1.626	159.37	4.08	-14.62
	O14 (P)	2.553	124.07		
	H17 (P)···				
	O16 (G)				
GP45	H17 (G)…	1.789	159.19	3.99	-13.24
	O14 (P)	2.390	137.03		
	H17 (P)····				
	O18 (G)				

Table 2 Length and angle of the hydrogen bonds, dipole moment, and complexation energy for the modelled complexes of glucose (G) and proline (P) with 1:1 stoichiometry.

The hydrogen bonds are denoted utilizing the atom numbering of glucose shown in Fig. 1 and the atom numbering of proline shown in Fig. 2; the molecule to which each atom belongs is indicated in parentheses.

The dipole moment changes with the sites of glucose to which proline is attached; it largely depends on the mutual orientations of all the OH groups in the complex.

The next step of the simulation considered two models in which two proline molecules interact with one glucose molecule (1:2 stoichiometry), as a first hypothesis for the formation of a network of H-bonds among the molecules present in the NADES mixture. The models are denoted as GP1P2 and GP1P34, where each P indicates one proline molecule and the numbers following them indicate the positions of the glucose molecule (Fig. 5) to which the given proline molecule is attached. Their optimized structures are presented in Figs. 6 and 7, respectively; Table 3 reports the lengths of their hydrogen bonds and their interaction energies.

In both complexes, there are two H-bonds between the glucose molecule and each of the proline molecules, with patterns analogous to those appearing in the 1:1 complexes. Table 4 compares the lengths of corresponding hydrogen bonds in 1:1 and 1:2 complexes. Comparison of the lengths in GP1P2 with those in GP1 and GP2 shows



Fig. 6 Optimized geometry of the GP1P2 model (stoichiometry 1:2).



Fig. 7 Optimized geometry of the GP1P34 model (stoichiometry 1:2).

	Parameters of h	Construction of the second		
Model	Hydrogen bond considered	Length (Å)	Angle (°)	(corrected for BSSE) (kcal/mol)
GP1P2 GP1P34	H17 (P1)····O23 (G) H24 (G)····O14 (P1) H17 (P2)····O12 (G) H13 (G)····O14 (P2) H17 (P1)····O23 (G) H24 (G)····O14 (P1) H17 (P34)····O16 (G)	1.764 2.031 1.793 2.107 1.759 2.042 1.738	158.76 132.19 158.77 127.06 159.17 131.61 167.19	-17.87 -24.05

Table 3 Lengths and angles of the hydrogen bond and complexation energy of the optimized geometries of the GP1P2 and GP1P34 models (1:2 stoichiometry).

Hydrogon	Length of hydrogen bond (Å)		Hydrogon	Length of hydrogen bond (Å)	
bond considered	In GP1P2	In GP1 or GP2	bond considered	In GP1P34	In GP1 or GP34
H17 (P1)····O23 (G)	2.031	1.764	H17 (P1)····O23 (G)	1.759	1.764
H24 (G)····O14 (P1)	1.764	2.031	H24 (G)…O14 (P1)	2.042	2.031
H17 (P2)····O12	1.793	1.793	H17 (P34)···· O16 (G)	1.738	1.735
H13 (G)····O14 (P2)	2.107	2.107	H15 (G)····O14 (P34)	1.767	1.767

 Table 4
 Comparison of the length of corresponding hydrogen bonds in 1:1 and 1:2 complexes of glucose and proline.

corresponding values, with a reversal of the lengths when the donor pertains to proline and when it pertains to glucose for P1. Comparison of the lengths in GP1P34 with those in GP1 and GP34 shows a reversal of the longer lengths for P1, and much closer lengths for the second proline in GP1P34 than in GP34.

The complexation energy of GP1P2 and GP1P34 are practically equal to the sum of the interaction energies of the corresponding 1:1 complexes (which would be -17.88 kcal/mol for GP1 and GP2, and -24.13 kcal/mol for GP1 and GP34). Although more verifications are advisable, this suggests the possibility of predicting the interaction energies of complexes with higher stoichiometry from the interaction energies of corresponding 1:1 complexes, as long as the proline molecules are not mutually interacting in the higher stoichiometry complex.

The dipole moment depends on the positions to which the proline molecules are attached to the glucose molecule. The dipole moment of the GP1P34 model (4.838 Debye) is double the dipole moment of the GP1P2 model (2.413 Debye); this difference can be ascribed to the different symmetries of the two models and to the fact that, in GP1P34, the proline molecules are basically on opposite sides with respect to the glucose molecule.

To gain a better understanding of the nature of the chemical bonds in the models, a non-covalent interactions (NCI) analysis was performed on the optimized models. NCI calculates the nature and location of the non-covalent interactions between molecules. The results are shown in Fig. 8.

The interactions corresponding to H-bonds appear clearly indicated for all the H-bonds identified in Fig. 4 and Table 2. The van der Waals interactions appear more evidently at the centre of the larger nine membered rings of GP23, GP34, and GP45. Repulsive interactions appear at the centre of the six membered rings in GP1 and GP2. This is consistent with the greater magnitude of the glucose-proline interaction energy in GP23, GP34, and GP45 with respect to GP1 and GP2 (Table 2).



GP45

Fig. 8 Non-covalent interactions (NCI) analysis for the calculated models with 1:1 glucose and proline stoichiometry. The *dark grey regions* represent hydrogen bonds, the *light grey regions* represent van der Waals interactions, and the *mid grey regions* represent repulsive interactions.

4. Conclusions

The previous sections presented an overview of the discovery, nature, consolidation in literature, and applications of NADES as greener alternative media in comparison to traditional solvents. They delineated perspectives regarding computational studies of NADES, which, coupled with experimental evidence, can help this new class of solvents to be viewed with reliability and credibility by the scientific community and the industry.

A computational study of glucose-proline NADES was also presented as an example. In this example, the computational simulations demonstrated the possibility of H-bonds between the hydrogen and oxygen atoms of glucose and proline, indicating the possibility of an H-bond network linking several glucose and proline molecules. This network may lead to unique spatial heterogeneity at the molecular level and may play a significant role in supporting chemical processes occurring within that NADES (used as a solvent) or mediated by it. More studies are necessary to unravel other aspects of the formation of glucose-proline NADES, such as the thermodynamics of the process.

The physicochemical properties determined by means of computational studies allow the researcher to estimate the interactions of a given NADES with future target-molecules (i.e., analytes of interest, such as bioactive metabolites or others depending on the goals of the research) and to predict solubility for several applications, such as catalysis, extractions, mobile phase modifier for chromatography, and others. The combination of computational and experimental investigations provides researchers with more knowledge about the structure and nature of these solvents, which fully relate to the purposes of green analytical chemistry and the demands of the contemporary world.

Acknowledgements

The authors gratefully acknowledge the financial support provided by the São Paulo Research Foundation (FAPESP, Grant Nos. 2013/08293-7, INCT BioNat No. 2014/50926-0, 2015/22338-9, and 2016/08179-8), the National Council for Scientific and Technological Development (CNPq, Grant Nos. 303581/2018-2, 305541/2017-0, 134790/2018-9 and INCT BioNat 465637/2014-0) Coordination for the Improvement of Higher Education Personnel (CAPES, Finance Code 001). The authors thank the referee for suggestions.

References

- Y. Dai, J.V. 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) 61–68.
- [2] M. Espino, M. de los Ángeles Fernández, F.J.V. Gomez, M.F. Silva, Natural designer solvents for greening analytical chemistry, Trends Anal. Chem. 76 (2016) 126–136.
- [3] M.C. Bubalo, S. Vidović, I.R. Redovniković, S. Jokić, Green solvents for green technologies, J. Chem. Technol. Biotechnol. 90 (2015) 1631–1639.
- [4] I. Lavilla, V. Romero, I. Costas, C. Bendicho, Greener derivatization in analytical chemistry, Trends Anal. Chem. 61 (2014) 1–10.
- [5] F. Pena-Pereira, A. Kloskowski, J. Namieśnik, Perspectives on the replacement of harmful organic solvents in analytical methodologies: a framework toward the implementation of a generation of eco-friendly alternatives, Green Chem. 17 (2015) 3687–3705.
- [6] K. Radošević, N. Ćurko, V.G. Srček, M.C. Bubalo, M. Tomašević, K.K. Ganić, I.R. Redovniković, Natural deep eutectic solvents as beneficial extractants for enhancement of plant extracts bioactivity, LWT Food Sci. Technol. 73 (2016) 45–51.
- [7] European Environment Agency, Towards a Green Economy in Europe. EU Environmental Policy Targets and Objectives 2010–2050, EEA Report No 8/2013, 2013.
- [8] A. Paiva, R. Craveiro, I. Aroso, M. Martins, R.L. Reis, A.R.C. Duarte, Natural deep eutectic solvents—solvents for the 21st century, ACS Sustain. Chem. Eng. 2 (2014) 1063–1071.
- [9] E. Durand, J. Lecomte, P. Villeneuve, From green chemistry to nature: the versatile role of low transition temperature mixtures, Biochimie 120 (2016) 119–123.
- [10] A.P. Abbott, R.C. Harris, K.S. Ryder, Application of hole theory to define ionic liquids by their transport properties, J. Phys. Chem. B 111 (2007) 4910–4913.

- [11] Y.H. Choi, J.V. 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) 1701–1705.
- [12] N.V. Plechkova, K.R. Seddon, Applications of ionic liquids in the chemical industry, Chem. Soc. Rev. 37 (2008) 123–150.
- [13] A.P. Abbott, G. Capper, D.L. Davies, R.K. Rasheed, V. Tambyrajah, Novel solvent properties of choline chloride/urea mixtures, Chem. Commun. (2003) 70–71.
- [14] M. Francisco, A. van den Bruinhorst, M.C. Kroon, Low-transition-temperature mixtures (LTTMs): a new generation of designer solvents, Angew. Chem. Int. Ed. 52 (2013) 3074–3085.
- [15] A.P. Abbott, D. Boothby, G. Capper, D.L. Davies, R.K. Rasheed, Deep eutectic solvents formed between choline chloride and carboxylic acids: versatile alternatives to ionic liquids, J. Am. Chem. Soc. 126 (2004) 9142–9147.
- [16] H. Monhemi, M.R. Housaindokht, A.A. Moosavi-Movahedi, M.R. Bozorgmehr, How a protein can remain stable in a solvent with high content of urea: insights from molecular dynamics simulation of Candida antarctica lipase B in urea: choline chloride deep eutectic solvent, Phys. Chem. Chem. Phys. 16 (2014) 14882–14893.
- [17] B.P. Wu, Q. Wen, H. Xu, Z. Yang, Insights into the impact of deep eutectic solvents on horseradish peroxidase: activity, stability and structure, J. Mol. Catal. B Enzym. 101 (2014) 101–107.
- [18] V.I.B. Castro, R. Craveiro, J.M. Silva, R.L. Reis, A. Paiva, A.R.C. Duarte, Natural deep eutectic systems as alternative nontoxic cryoprotective agents, Cryobiology 83 (2018) 15–26.
- [19] Y. Dai, G.J. Witkamp, R. Verpoorte, Y.H. Choi, Natural deep eutectic solvents as a new extraction media for phenolic metabolites in *Carthamus tinctorius* L, Anal. Chem. 85 (2013) 6272–6278.
- [20] Z. Wei, X. Qi, T. Li, M. Luo, W. Wang, Y. Zu, Y. Fu, Application of natural deep eutectic solvents for extraction and determination of phenolics in Cajanus cajan leaves by ultra performance liquid chromatography, Sep. Purif. Technol. 149 (2015) 237–244.
- [21] Q. Zhang, K.O. Vigier, S. Royer, F. Jérôme, Deep eutectic solvents: syntheses, properties and applications, Chem. Rev. 41 (2012) 7108–7146.
- [22] E.L. Smith, A.P. Abbott, K.S. Ryder, Deep eutectic solvents (DESs) and their applications, Chem. Rev. 114 (2014) 11060–11082.
- [23] F.J.V. Gomez, M. Espino, M.A. Fernández, M.F. Silva, A greener approach to prepare natural deep eutectic solvents, ChemistrySelect 3 (2018) 6122–6125.
- [24] A.P. Abbott, J.C. Barron, G. Frisch, K.S. Ryder, A.F. Silva, The effect of additives on zinc electrodeposition from deep eutectic solvents, Electrochim. Acta 56 (2011) 5272–5279.
- [25] D.V. Wagle, H. Zhao, G.A. Baker, Deep eutectic solvents: sustainable media for nanoscale and functional materials, Acc. Chem. Res. 47 (2014) 2299–2308.
- [26] T. Jeliński, P. Cysewski, Application of a computational model of natural deep eutectic solvents utilizing the COSMO-RS approach for screening of solvents with high solubility of rutin, J. Mol. Model. 24 (2018) 180–197.
- [27] M. de los Ángeles Fernández, J. Boiteux, M. Espino, F.V. Gomez, M.F. Silva, Natural deep eutectic solvents-mediated extractions: the way forward for sustainable analytical developments, Anal. Chim. Acta 1038 (2018) 1–10.
- [28] C.S. Funari, A.T. Sutton, R.L. Carneiro, K. Fraige, A.J. Cavalheiro, V.S. Bolzani, E.F. Hilder, R.D. Arrua, Natural deep eutectic solvents and aqueous solutions as an alternative extraction media for propolis, Food Res. Int. 125 (2019) 108559.

- [29] P. Pisano, M. Espino, M. de los Ángeles Fernández, M.F. Silva, A.C. Olivieri, Structural analysis of natural deep eutectic solvents. Theoretical and experimental study, Microchem. J. 143 (2018) 252–258.
- [30] G. Garcia, M. Atilhan, S. Aparicio, An approach for the rationalization of melting temperature for deep eutectic solvents from DFT, Chem. Phys. Lett. 634 (2015) 151–155.
- [31] J. Singh, N.B. Singh, Solidification and computational analysis of *o*-nitroaniline-α-naphtol eutectic system, Fluid Phase Equilib. 386 (2015) 168–179.
- [32] A. Klamt, F. Eckert, COSMO-RS: a novel and efficient method for the a priori prediction of thermophysical data of liquids, Fluid Phase Equilib. 172 (2000) 43–72.
- [33] R.F.W. Bader, Atoms in Molecules: A Quantum Theory, first ed., Clarendon Press, Oxford, 1990.
- [34] I.Y. Zhang, J. Wu, X. Xu, Extending the reliability and applicability of B3LYP, Chem. Commun. 46 (2010) 3057–3070.
- [35] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G.A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H.P. Hratchian, A.F. Izmaylov, J. Bloino, G. Zheng, J.L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J.A. Montgomery Jr., J.E. Peralta, F. Ogliaro, M. Bearpark, J.J. Heyd, E. Brothers, K.N. Kudin, V.N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Ren-dell, J.C. Burant, S.S. Iyengar, J. Tomasi, M. Cossi, N. Rega, N.J. Millam, M. Klene, J.E. Knox, J.B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, R.L. Martin, K. Morokuma, V.G. Zakrzewski, G. Voth, P. Salvador, J.J. Dannenberg, S. Dapprich, A.D. Daniels, O. Farkas, J.B. Foresman, J.V. Ortiz, J. Cioslowski, D.J. Fox, Gaussian 16 (Revision A.03), Gaussian, Inc., Wallingford, CT, 2016.
- [36] E.R. Johnson, S. Keinan, P. Mori-Sánchez, J. Contreras-García, A.J. Cohen, W. Yang, Revealing noncovalent interactions, J. Am. Chem. Soc. 132 (2010) 6498–6506.
- [37] J. Contreras-García, E.R. Johnson, S. Keinan, R. Chaudret, J.P. Piquemal, D.N. Beratan, W. Yang, NCIPLOT: a program for plotting noncovalent interaction regions, J. Chem. Theory Comput. 7 (2011) 625–632.
- [38] S. Boys, F. Bernardi, The calculation of small molecular interactions by the differences of separate total energies. Some procedures with reduced errors, Mol. Phys. 19 (1970) 553–566.

This page intentionally left blank