

# Computational Analysis on the Microstructure of Natural Deep Eutectic Solvent – A Review

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Over the last few years, the experimental and theoretical investigation regarding natural deep eutectic solvent (NADES) has gained more attention to unravel the behaviour behind the formation of eutectic solvent. The application domain of this solvent is also increased at the same pace, yet the mechanism of its formation is barely elucidated. The fundamental studies are limited to certain class of compounds which did not cover all the possible NADES species. This review aims to shed light on the formation mechanism of this novel solvent, which covers organic salt, organic acids, and alcohol-based NADES. The microstructure of NADES is found to form an extensive hydrogen bond network, considered one of the factors for this unique phenomenon. The hydrogen bonds are found to form at random hydrogen bond donor (HBD) and hydrogen bond acceptor (HBA) side, whereby the pattern is considerably similar for most classes of NADES. The molar ratio and species involved within the system also affect the resulting NADES, especially their physicochemical properties. This review provides insight into the binary and ternary system of NADES by highlighting the recent findings focusing on computational and theoretical work that utilise the quantum chemical and molecular dynamic approach.

## 1. Introduction

Deep eutectic solvent (DES) and natural deep eutectic solvent (NADES) are the novel solvents that generally hold the same fundamentals concept. The term eutectic is defined as a mixture of two or more components normally consisting of hydrogen bond donor (HBD) and hydrogen bond acceptor (HBA) that are miscible in each other without forming any chemical reaction. Given the right the molar ratio, it will lead to depression of melting point of the mixture, resulting in a system that has a low melting point than the individual component (Hansen et al., 2020). The resulting mixtures are normally liquid at room temperature (Cicci et al., 2017). NADES generally comprises of natural resources-based compounds (Liu et al., 2018), which are distinguishable from compounds used in DES. One of the advantages of NADES is, the 'green' character of this solvent in not compromised (Gómez et al., 2019). In fact, NADES is considered very safe because it possesses very low toxicity, easy waste disposal and is biodegradable (Paiva et al., 2014). Previous studies have reported a wide range of NADES applications. NADES has been applied in biomedical applications (Liu et al., 2018), enzymatic reactions and pharmaceuticals (Vanda et al., 2019), extraction of phytochemicals (Che Zain et al., 2021), phase change materials (Kahwaji and White, 2018), gas absorption (Isaifan and Amhamed, 2018) and synthesis of nanoparticles (Karimi et al., 2016). The synthesis process of NADES required less energy, where it can be as simple as heating and stirring the mixture (Santana et al., 2019). Although previous studies have reported the benefit and application of NADES in various research area, the understanding of the fundamental concept of NADES at the molecular level is still scarce. The factors involved in the formation mechanism of this solvent remain to be elucidated. The selection of NADES components is hard to predict because there are unlimited possibilities for NADES species. Computational-aided tools are the best option to study the interaction behind this unique phenomenon. The common method such as density functional theory (DFT) and molecular dynamic (MD) simulation required huge effort to study this mixture. A recent study have reported that the cause of the

melting point depression is due to the extensive of hydrogen bonding network within the system (Stefanovic et al., 2017) but the study is mostly limited to a certain group of compounds. Hydration was also considered when synthesizing the NADES, due to its high viscosity in dry condition. Certain amount of water is normally added into the NADES as a ternary component, to tailor its abilities for targeted applications, such as heat and mass transfer abilities (Alcalde et al., 2019).

The contribution of the hydrogen bond network as one of the factors for the formation of NADES is barely elucidated. It is difficult to understand this phenomenon by making a generalized concept of how it occurred, because NADES possesses a wide range of chemicals constituents with distinct molecular structure, functional groups, chemicals, and physical properties. This review will provide an overview to understand a certain group of NADES that incorporates computational techniques limited to DFT and MD. The formation mechanism of liquid NADES in terms of molecular arrangement, focusing on the intermolecular hydrogen bond within the system is discussed. This review also highlights the binary mixture of NADES and ternary mixture, which is limited to the addition of water into the system.

## 2. Computational analysis of molecular structures and interactions

Computational analysis utilizing DFT and MD are the common methods to understand the bonding interaction and energy deep down into molecular level. These techniques have been applied by many researchers to understand the behaviour for a certain class of NADES. This section will discuss three classes of NADES to gather the information regarding hydrogen bonding interaction within the system.

### 2.1 Organic salt-based NADES

The most typical organic salt-based NADES are made up of choline chloride (Abbott et al., 2003) and betaine (Fanali et al., 2020) which normally incorporate with urea (Rain et al., 2021). Since NADES can have an unlimited selection of compounds, other organic salt species were also introduced into this system (Wu et al., 2021). Ashworth et al., (2016) were found a large number of hydrogen bonds within choline chloride/ urea (1:2) NADES system using density functional theory. This study provides a comprehensive view on the hydrogen bonds by analyzing each of the possible pairs of atoms that can create hydrogen bonding. Three types of hydrogen bonds were characterized namely doubly ionic hydrogen bond (bond between choline chloride ion pairs), anionic hydrogen bond (bond between urea and chloride ions) and cationic hydrogen bonds (bond between choline cation and urea). The wide range of hydrogen bonds revealed that there is a competition between the lower number of strong hydrogen bonds and higher number of weak hydrogen bonds. This competition will lead to the formation of the liquid structure. In choline cation structure, the Ashworth et al. (2016) observed a strong interaction occurs between C-H donor at ammonium head group, with Cl, but not with O-H at alkyl chain. There is competition between C-H...Cl with N-H...Cl in urea, albeit N-H is known as good hydrogen bond donor than C-H. In addition, one of the important roles of urea in this system is, it will sit between the charge molecule to dissociate the ions within the liquid (Ashworth et al., 2016).

Another common method to describe the interaction within DES or NADES is by using molecular dynamic simulation by giving an optimized structures and generates a visualization for the liquid structure of this system. In addition, radial distribution function (RDF) calculation will help to further understand the interaction of hydrogen bond between molecules in the system by showing the possibilities of finding atoms from a tagged atoms at a certain radius. Fetisov et al., (2018) run a simulation using first principle molecular dynamic (FPMD) method for choline chloride and urea NADES. In this study, they investigate the effect of temperature for different condition of choline chloride/urea NADES (anhydrous and hydrated). In general, different temperature doesn't give significant influence in the molecular interaction pattern in this NADES. Addition of water instead will give certain effect on the bonding interaction and molecular arrangement in the system. Based on RDF of anhydrous choline chloride/urea (1:2), it shows that the strongest interaction appeared in Cl-urea, which is contradicted with the finding described by Ashworth et al., (2016) and Rain et al., (2021). In the case of hydrated form of choline chloride/urea/water (1:2:3), there are strong interaction occur between water-water and Cl-water, which is different from its anhydrous form. As water introduced into the system, it will disrupt the hydrogen bonds between Cl-urea where the water molecules replaced the urea molecules. In general, Cl<sup>-</sup> is preferentially to form hydrogen bond with urea in anhydrous form but will form hydrogen bond with water in hydrated form (Fetisov et al., 2018). Sapir and Harries (2020) utilised a hydrated form of choline chloride/urea DES and highlighted two conditions, water-in-DES and DES-in-water as shown in Figure 1a. With the aid of molecular dynamic simulation, they managed to elucidate the arrangement of molecules in different water content. Based on centre of mass RDF results, anhydrous choline chloride/urea (1:2) showed a stronger interaction between Cl-urea, but once the water was introduced into the system, even at 5 %, the Cl<sup>-</sup> shift its bonding interaction to Cl-water significantly. There are obvious changes observed, where the addition of water molecules changes the molecular arrangement of the whole system. Initially, the distance between Cl-Cl is larger because of the bulky

structure of choline and urea. When the hydration is gradually increased and large enough, the water molecule will pull the chloride atoms closer together and create a water bridging as shown in Figure 1b, subsequently forming an extensive hydrogen bond within the system. This phenomenon is very much in good agreement with study provided by Fetisov et al. (2018) and Gao et al. (2018). Overall, as the water content gradually increases, the nanostructure of the liquid indirectly turns hydrated (Gao et al., 2018) while keeping their basic configuration in term of intermolecular distance (Sapir and Harries, 2020). The study of these two conditions is crucial because the anhydrous form NADES are normally viscous. Therefore, addition of certain amount of water will help to reduce the viscosity and can be tailored to meet the desired applications.

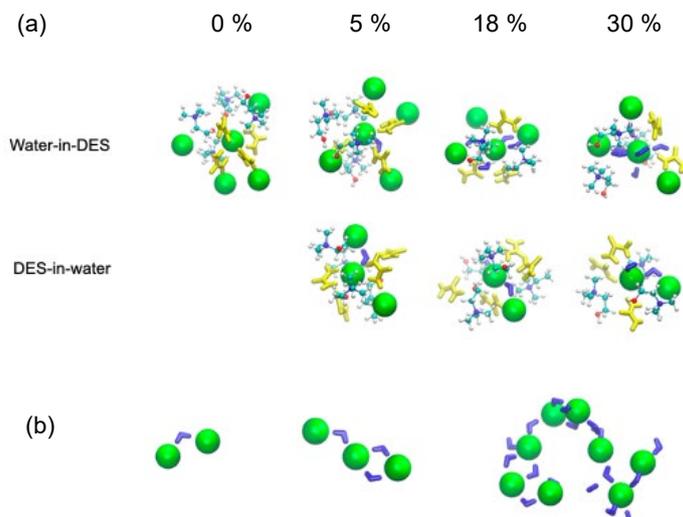


Figure 1: (a) Structural representation of liquid choline chloride/urea in different water content. (b) Formation of water bridging, and formation of chloride cluster. Reprinted with permission from Sapir and Harries (2020). Copyright 2020 American Chemical Society

Rain et al., (2021) provide a study using DFT, of different class of compound as HBD combined with choline chloride as HBA. Comparing the hydrogen bonds between choline chloride/oxalic acid (1:1) and choline chloride/malic acid (1:1), both shows a strongest interaction between  $\text{OH}\cdots\text{Cl}$ . This is because both acids have OH as donating group. However, choline chloride/oxalic acid is less stable because it forms intramolecular hydrogen bond with its HBA,  $\text{OH}\cdots\text{O}=\text{C}$ , whereby interfere the hydrogen bond strength with chloride. Choline chloride/malic acid on the other hand is more stable because the long alkyl chain leads toward low energy intramolecular hydrogen bond. Besides, the strongest hydrogen bond identified in choline chloride/glycerol (1:2) and choline chloride/phenol (1:2) were also  $\text{OH}\cdots\text{Cl}$ . Choline chloride/ glycerol in this case is more stable because it consists of many HBD moieties which can provide large hydrogen bond network (Rain et al, 2021). Hence, in the case of mixing choline chloride with sugars or alcohol-based compounds, the chloride preferred to create a bonding with OH donor sites rather than interaction with its counter ion. Nonetheless, the interaction that occurred in this system representing the liquid NADES is not provided here.

## 2.2 Alcohol-based NADES

Another class of NADES is alcohol-based NADES. Alizadeth et al., (2020), investigated the choline chloride and ethylene glycol-based NADES and found that by addition of ethylene glycol composition increased the distance between Cl-Cl. The atom-atom RDF pattern of choline chloride/ethylene glycol (1:1 and 1:2) and choline chloride/ethylene glycol/water (1:2:1) NADES showed that interaction between Cl- and cations moieties is found first, only then with hydroxyl moieties in choline-chloride interactions. According to the RDF peaks, these interactions showed almost the same possibilities that barely distinguishable, indicating that there is a competition to form hydrogen bond between cation and hydroxyl moieties of choline molecules. Increasing the amount of ethylene glycol will increase the hydrogen bond network in the system. This situation might be due to the large number of HBD and HBA sites of ethylene glycol. Furthermore, the addition of water weakens the interaction between ethylene glycol with both cations and anions but increase the interaction of water-Cl. Water showed almost similar behaviour as in the choline chloride/urea/water system (Sapir and Harries, 2020). The addition of water also increases ethylene glycol-ethylene glycol interaction. Overall, the RDF pattern only showed slight effect on the bonding interaction whether by changing the ethylene glycol composition nor by

addition of water (Alizadeth et al., 2020). In other study, Wu et al. (2021) investigated the behaviour of ethylene glycol in combination with tetraethyl ammonium chloride and tetraethyl ammonium bromide at different molar ratio of ethylene glycol. The increased amount of ethylene glycol reduced the interaction between cations and anion, and the hydrogen bond network among ethylene glycol (Wu et al., 2021). This phenomenon is a slightly different from the choline chloride/ethylene glycol NADES reported by Alizadeth et al., (2020). Complete molecular interactions regarding this system, however, are not fully described.

Other common alcohol-based NADES consists of glycerol. Aissaoui et al. (2017) have made a microstructural investigation of glycerol-based NADES in combination with different bromide and chloride salt. The simulation of chemical interaction showed that, all Cl<sup>-</sup> and Br<sup>-</sup> interacted with H atom of glycerol, forming Cl<sup>•••</sup>HO and Br<sup>•••</sup>HO hydrogen bond. Different situation was observed in glycerol-N,N-diethylenethanolammonium chloride NADES, where the O atom in glycerol molecule interacted with H atom in choline cation, producing an extra one hydrogen bond, forming O<sup>•••</sup>HO hydrogen bond (Alizadeth et al., 2020). A recent study of glycerol-based NADES was conducted by Turner and Holbrey (2019), where they investigated the hydrogen bonding network of choline chloride/glycerol NADES at a different composition of glycerol. According to the centre of mass RDF pattern, no significant difference observed between choline chloride/ glycerol 1:1 and 1:2 molar ratio, indicating that there are not many changes happened in the local structure. Each molar ratio showed that, the interaction between choline-chloride dominated at the shortest distance within the system. The interaction between glycerol-chloride was also observed but at lower probabilities at almost the same distance. Analysis of atom-centred RDF of choline chloride/glycerol (1:2) NADES, showed the highest interaction between chloride and hydrogen atom of glycerol forming Cl<sup>•••</sup>HO. Chloride also interacted ionically with nitrogen atoms of choline, and also with hydrogen atoms on the hydroxy moieties of choline. However, the distance for this interaction was quite far between each other, where chloride was preferentially attracted to hydroxyl moieties of choline at shortest distance forming Cl<sup>•••</sup>HO (Turner and Holbrey, 2019). This is similar to other alcohol-based NADES reported by Alizadeth et al. (2020).

A more recent study of novel NADES consisting of terpene-based (thymol, naphthol and menthol) was conducted by Panda and Bhargava (2022) using molecular dynamic simulations. This class of compound can be classified under alcohol-based NADES due to the presence of hydroxyl moieties. In naphthol/menthol (1:2) NADES, the self-interaction of naphthol-naphthol gives higher probabilities than naphthol-menthol interaction according to the centre of mass RDF results, which proves that self-interaction still dominates even after the formation of NADES. Different situation occurs in thymol/menthol (1:2) NADES, where interaction between thymol and menthol gives the highest probability compared to self-interactions. Based on atom-atom RDF, it appeared that the hydrogen atom of thymol has higher interaction with the oxygen atom of menthol forming H<sup>•••</sup>OH in thymol/menthol NADES. Besides, stronger interaction occurs between hydrogen of naphthol with oxygen of menthol which also forming H<sup>•••</sup>OH in naphthol/menthol. This proves that the hydrogen bond plays the main roles in this formation mechanism of NADES in the case of non-ionic compound NADES (Panda and Bhargava, 2022). Another research on terpene-based NADES was conducted by Fan et al. (2021) and mix it with organic acids. The atom-atom RDF of camphor/formic acid (1:1) NADES shows only one intense peak indicates the hydrogen bond interaction between oxygen atom of camphor and hydrogen atom of formic acid. Menthol/acetic acid (1:1) shows two probabilities of hydrogen bond interaction appeared at the same distance, where the highest interaction is between oxygen of menthol and hydrogen acetic acid and another one is the interaction between hydrogen of menthol and oxygen of acetic acid. Same patterns occur in atom-atom RDF of menthol/ $\beta$ -citronellol (1:1) NADES, but the peak is barely disguisable. The highest peak is the interaction between oxygen atom of menthol and hydrogen atom of  $\beta$ -citronellol, and the lowest peak is interaction between hydrogen atom of menthol and oxygen atom of  $\beta$ -citronellol. Another double site hydrogen bond interaction also appeared in thymol/ $\beta$ -citronellol (1:1) NADES. In this system, the probability difference for the interactions is very significant. The highest interaction is between hydrogen atom of thymol and oxygen atom of  $\beta$ -citronellol, and the lowest is interaction between oxygen atom of thymol and hydrogen atom of  $\beta$ -citronellol. Finally, a unique pattern observes in RDF of menthol/ lactic acid (1:1) NADES, where there are multiple sites for the formation of hydrogen bonds, Surprisingly, the probability of the hydrogen bond found around the same distance. The highest peak observed is the interaction between oxygen atom of menthol and hydrogen atom of lactic acid. The other peak is the interaction between hydrogen atom of menthol and oxygen atom of lactic acid at different positions and orientations (Fan et al., 2021). In general, all the interaction will form hydrogen bonding HO<sup>•••</sup>H in non-ionic compound NADES (Panda and Bhargava, 2022)

### 2.3 Organic acid-based

An investigation of structural properties of organic acid-based NADES was performed by Bonab et al. (2021). They investigated the structure and hydrogen bond interaction of choline chloride/phenyl propanoic acid NADES at different amount of phenyl propionic acid. The atom-atom RDF of the overall system shows that, interactions

of choline-chloride, phenyl propionic acid-chloride and phenyl propionic acid-phenyl propionic acids resulted in significant probability at shortest distance. Interaction between specific atoms of choline chloride and phenyl propionic acid can be referred in Figure 2. Increasing the phenyl propionic acid amount, will increase the interactions between chloride and H4 of phenyl propionic acid and between chloride and H14 of choline. Both of the interactions will form  $\text{Cl}\cdots\text{HO}$  hydrogen bonding. Interaction of H14 of choline and O1 of phenyl propionic acid also show the same pattern, but the probability is very low compared to the other and does not really contribute toward the formation of NADES. A different case occurs among phenyl propionic acid molecules, where intermolecular hydrogen bonds are very intense at the lowest amount of phenyl propionic acid. Intramolecular hydrogen bonds between phenyl propionic molecules are rather different where it will increase with the increasing amount of phenyl propionic acid. Both intermolecular and intramolecular interactions will form  $\text{OH}\cdots\text{O}$  hydrogen bond, but the probability of intramolecular interaction was found to be lower than the intermolecular hydrogen bonds (Bonab et al., 2021).

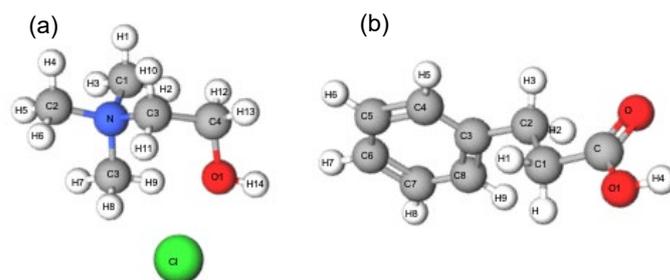


Figure 2: Molecular structures of (a) choline chloride and (b) phenyl propionic acid

### 3. Conclusions

Choline chloride-based and other organic salt-based NADES has gained more attention from the community in the scientific area over the years. The exploration of other-based compound NADES comes after and slowly penetrate into this unique system. The microstructural investigation of this solvent revealed that, hydrogen bonding was the primary factor for this eutectic behaviour to form, especially for non-ionic compound NADES. The bonding interaction is usually within the hydrogen bond donor and hydrogen bond acceptor site, but not all sites involve forming hydrogen bond. It is difficult to specify which molecules belong to HBA or HBD, because some molecules can act as both. The pattern regarding hydrogen bonding formation is about the same for all classes of compound. As the hydrogen bond gets stronger, a more stable NADES can be formed. The binary and ternary systems show some distinction. Normally, binary systems will have a large distance between each other due to their large molecular structure. Ternary system in contrast will fill the voids within the system and act as a spacer which then pulls certain molecules together, such as water, subsequently create more extensive hydrogen bonds. Therefore, a more stable NADES and less viscous NADES can be formed. Laying out a more generalized concept regarding the formation mechanism of NADES is a challenging and on-going process, as different molar ratios and different species involved will affect the resulting solvent. Classifying the NADES into several groups can give some idea about its behaviour. More fundamental studies regarding its formation covering other compounds, such as glucose-based and amino acid-based, can be helpful to understand this system. A strong fundamental concept of this solvent can lead to a more versatile solvent design and create a more extensive application domain.

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