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Reference:

Kovács Attila, Billen Pieter, Cornet Iris, Wijnants Marc, Neyts Erik.- Modeling the physicochemical properties of natural deep eutectic solvents : a review
Chemsuschem - ISSN 1864-5631 - Weinheim, Wiley-v c h verlag gmbh, 2020, p. 1-17
Full text (Publisher's DOI): https://doi.org/10.1002/CSSC.202000286
To cite this reference: https://hdl.handle.net/10067/1688510151162165141

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To be cited as: *ChemSusChem* 10.1002/cssc.202000286

Link to VoR: https://doi.org/10.1002/cssc.202000286

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Modeling the Physicochemical Properties of Natural Deep Eutectic Solvents – A Review

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May 5, 2020

Abstract

Natural deep eutectic solvents (NADES) are mixtures of naturally derived compounds with a significantly decreased melting point due to the specific interactions among the constituents. NADES have benign properties (low volatility, flammability, toxicity, cost) and tailorable physicochemical properties (by altering the type and molar ratio of constituents), hence they are often considered as a green alternative to common organic solvents. Modeling the relation between their composition and properties is crucial though, both for understanding and predicting their behavior. Several efforts were done to this end, yet this review aims at structuring the present knowledge as an outline for future research. First, we reviewed the key properties of NADES and relate them to their structure based on the available experimental data. Second, we reviewed available modeling methods applicable to NADES. At the molecular level, density functional theory and molecular dynamics allow interpreting density differences and vibrational spectra, and computation of interaction energies. Additionally, properties at the level of the bulk media can be explained and predicted by semi-empirical methods based on ab initio methods (COSMO-RS) and equation of state models (PC-SAFT). Finally, methods based on large datasets are discussed; models based on group contribution methods and machine learning. A combination of bulk media and dataset modeling allows qualitative prediction and interpretation of phase equilibria properties on the one hand, and quantitative prediction of melting point, density, viscosity, surface tension and refractive indices on the other hand. In our view, multiscale modeling, combining the molecular and macroscale methods, will strongly enhance the predictability of NADES properties and their interaction with solutes, yielding truly tailorable solvents to accommodate (bio)chemical reactions.

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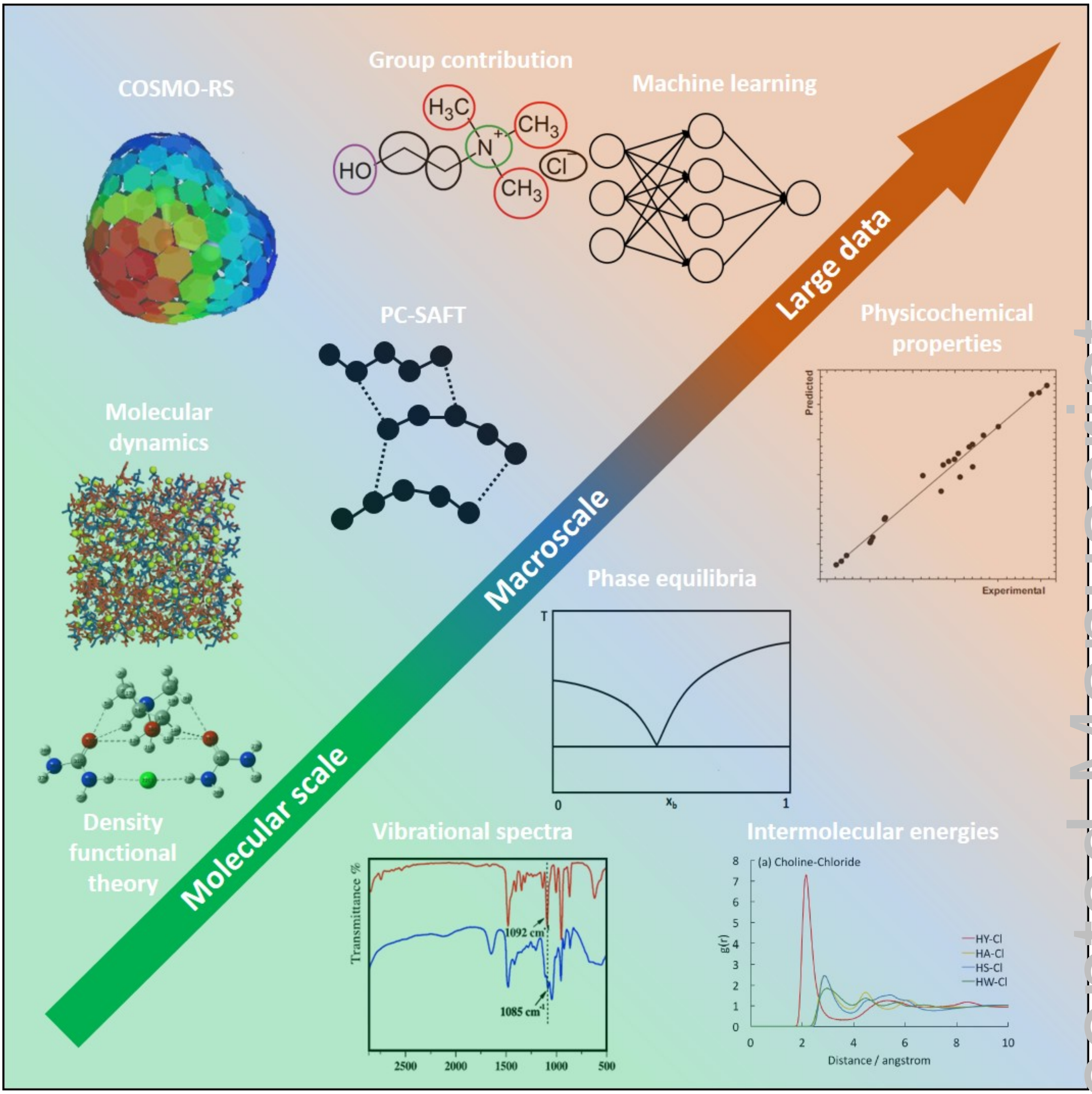

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Attila Kovács is PhD student of applied engineering. His research interest is the special effects of natural deep eutectic solvent as media on enzymatic reactions. His research goal is the description, modelling and prediction of these effects. He holds a MSc in chemical engineering from Budapest University of Technology and Economics (Hungary).

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1 Introduction

Deep eutectic solvents (DES) were first reported in 2001, as novel solvent class based on eutectic systems and potential alternative to ionic liquids, when Abbot et al. observed significant decrease in the melting point of metal chlorides and quaternary ammonium salts.[1] These DES showed many common characteristics with ionic liquids (IL) and their melting point was below room temperature in some cases. Although the term DES was introduced in 2003, no clear agreement was made upon its definition. The formerly published articles set up different requirements for DES: Zhang et al. descripted DES as the composition of two or more components, which are interacting through a hydrogen bond interaction, forming a eutectic mixture.[2] Francisco et al. connected the lowered melting point to the lowered entropic difference of the phase transition.[3] Smith et al. defined the components as Lewis or Brønsted acids and bases.[4] Paiva et al. only set the requirement of the significantly lowered melting point, compared to the melting point of the individual components.[5] Due to the unclear definition, we introduce only their general characteristics. DES are a mixture of two or more compounds which are associating through hydrogen bonding. The most frequently studied DES are formed by a quaternary ammonium salt and a metal salt or a hydrogen bond donor (HBD) component. The salt components in DES typically have low lattice energy. The components form a hydrogen bonding network, which increases the system's stability and in case of ionic constituents, allows the charge delocalization. The decreased melting point is the result of these effects. Figure 1 illustrates the hydrogen bonding interactions on the most commonly studied DES, the mixture of choline chloride and urea.

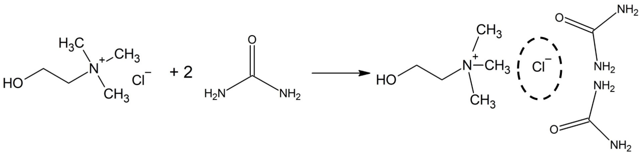

Figure 1: Deep eutectic solvent preparation from choline chloride (hydrogen bond acceptor component) and urea (hydrogen bond donor component). The dashed circle represents the complex hydrogen bonding formed between the constituents.

Natural deep eutectic solvents (NADES) were reported in 2011 by Choi et al., as a subclass of DES.[6] NADES are composed of na5turally derived components, such as the primary metabolites, carboxylic and amino acids, choline chloride, sugars or urea. Choi et al. discussed the possibility of NADES presence in living organisms as a third liquid phase next to water and lipids, what could rationalize the biosynthesis of poorly water soluble macromolecules in cells that are otherwise aqueous environments, or the survival of organisms in arid environments. Changing common organic solvents to NADES have many benefits, as the latter ones are non-volatile and non-flammable.[5] Compared to ionic liquids, NADES are cheaper with better biodegradability and lower toxicity. NADES can be manufactured with 100% atom economy and they are less sensible to impurities than ILs. The potential of NADES was already proven in organic reactions, extraction processes and electrochemistry applications.[2] The most promising field for NADES is the biochemical industry, as NADES provide not only a green media for enzymatic reactions, but they can increase the efficiency of certain biocatalytic reactions.[7] The eutectic mixtures seem to modify both the reactivity and stability of enzymes compared to conventional media. The growing interest in NADES is also reflected by the number of academic publications and citations (See Fig. 2.).

The biggest potential of DES and NADES is their application as designer solvents.[3] Designer solvents are systems of which the properties can be tailored according to the application. In DES, the hydrogen bonding network between the components defines the behavior of the given mixture to a large extent. Therefore the desired properties can be achieved by changing the components used and their molar ratio. Currently, the relation between the composition and the properties of NADES is not described adequately and the development of new systems done through trial-and-error. Given the lack of generic design methodology to predict the relevant properties of novel NADES systems, such as viscosity, surface tension or solubility, these eutectics cannot be used as "designer solvents". The relation between NADES structure, properties and the possible application is conceptually illustrated in Fig. 3. Recognizing the importance of the subject various studies investigated the possibility of modeling NADES behavior, both in view of a better understanding of structure-property relations, and in order to predict the properties of these systems. Despite the high number of publications related to this field, to the best of our knowledge, no review structuring the recent advances in the modeling of NADES' behavior was reported.

The aim of this review is therefore to introduce the current state of understanding on the structure-property relations of NADES and the advances in its modeling. This paper gives a general overview of the available

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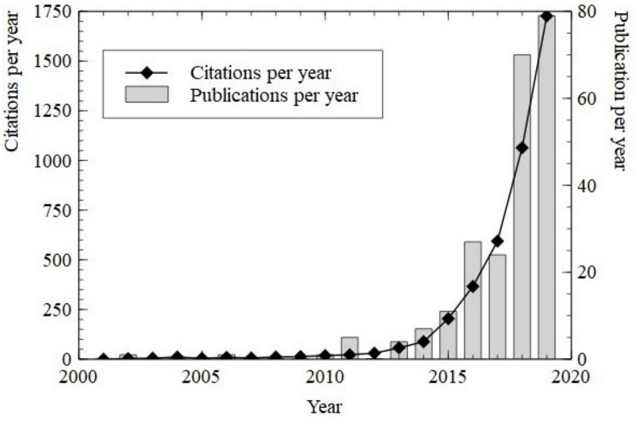

Figure 2: Number of yearly publications (left vertical axis), and yearly citations (right vertical axis), using the keywords “natural deep eutectic solvent” OR ” natural deep eutectic solvents” OR “NADES” (Source: Web of Science; date of search: 2019.12.05).

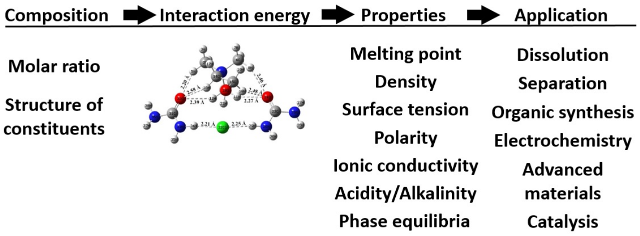

Figure 3: Structure-properties-application relation (Interaction energy of choline chloride and urea by Zhu et al.[8]

methods to researchers and developers, who are new to the field of modeling physicochemical properties. First, we discuss the relevant physicochemical properties of NADES, their relation to the composition and general considerations to tailor the properties of systems that were explored thus far. o In the second part, we introduce the available methods to model NADES behavior, starting at the level of molecular interactions, with subsequently the prediction of bulk properties of NADES such as density or viscosity, and finally the analysis of larger datasets with machine learning methods.

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2 Structure-property relations of NADES

The special properties of NADES are the result of the intermolecular hydrogen bonding system among the components. The strength of this interaction determines to a large extent the physicochemical properties of the eutectic mixture and it depends on the structure and ratio of the components in the mixture. To design the properties of NADES, the relation between the properties and composition of the mixture has to be known. For a given application, the tailored medium has to possess good solvation, transport properties and its use should be safe. Nonetheless, the additional effects of NADES on the reaction (e.g., side reactions, inhibition, catalytic effect) have to be considered as well. During development, there are many relevant properties to take into account, such as melting point, density, viscosity, polarity, ionic conductivity, acidity or alkalinity, and surface tension. The solubility of different chemicals in the mixture is for obvious reasons also a key aspect. The water content of the eutectics has a significant effect on all the properties, therefore it will be discussed in more detail, along with the effect of NADES on (bio)catalytic reactions as a major application domain.

2.1 Melting point

The application of an eutectic system is determined by the eutectic point: the lowest melting point of the system and its associated composition. However, the temperature of a specific application determines an allowed composition range for potential use of a given NADES (See Fig. 4). Although many NADES were reported in the literature,[2;9;10;11;12;13;14] systems with a melting point below room temperature are still scarce. NADES containing amides, carboxylic acids and sugar-derived polyols with organic salts, often have melting points below room temperature.

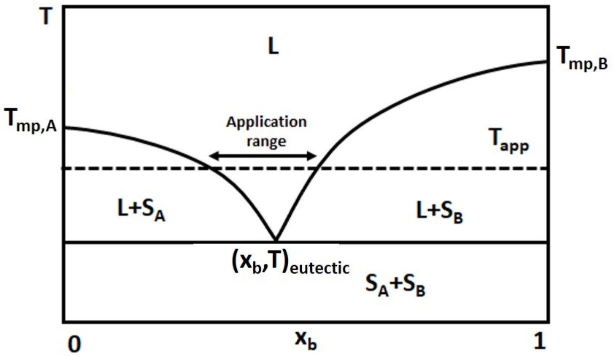

Figure 4: T-x phase diagram of simple eutectic behavior: the diagram shows the change of the system's melting point (T) as the function of molar ratio of constituent B (x_B) in the mixture. $T_{mp,A}$, $T_{mp,B}$ are the melting points of the pure A and B constituents, T_{app} is the temperature of the given application, L is the liquid phase, while S_A and S_B are the solid phases of constituent A and B. ($x_{B,T}$)eutectic indicates the eutectic composition and temperature of the mixture.

Zhang et al. comprehensively studied the empirically observed relation between structure and melting point.[2] HDB components with lower molecular weight yields a larger melting point depression. The asymmetry of the cation decreases the melting point (due to smaller lattice energies), while the increasing electron affinity of the anion also has a decreasing effect on melting point (as this yields stronger hydrogen bonds between the two constituents). The addition of a ternary component to the system can also lead to a decrease of the melting point.[13;14] By comparing the eutectic points of mixtures with organic salts and mono- or dicarboxylic acids, it was found that the complexation of the anion requires two molecular carboxyl groups.[2] These observations are in line with the general assumption that stronger interactions between the components result in a greater decrease of the melting point.

In the NADES of choline chloride and carboxylic acids, the lattice energies of the HBD does not show a correlation with the melting point depression, but the HBD with the lowest molecular weight is associated to the largest melting point depression.[2] From this observation, Abbott et al. one can assume that the lattice energy of the HBD only relates to the HBD-anion interaction, therefore the melting point depression is related to the mixing entropy only.[9] Consequently, in a first approximation the melting point depression is a measure of the entropy change, i.e., the magnitude of the depression relates to the increase of entropy change during mixing.

In this view, we suggest an approach based on the method of Krossing et al. (which was developed to rationalize the low melting points of ionic liquids) to describe the relation between molecular interactions of

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constituents and the change of the melting point.[15] During the melting (fusion) of the NADES constituents, both the enthalpy (H) and the entropy (S) of the system change. These changes can be described by the change of Gibbs free energy:

$$\Delta G = \Delta H - T \cdot \Delta S \tag{1}$$

At the melting temperature of the eutectic, the ΔG of the melting is zero:

$$\Delta G_f usion^t otal(T_e utectic) = 0 \tag{2}$$

At other temperatures, the value of ΔG indicates, whether the solid ($\Delta G > 0$) or the liquid ($\Delta G < 0$) state is the thermodynamically stable (See Fig 5).

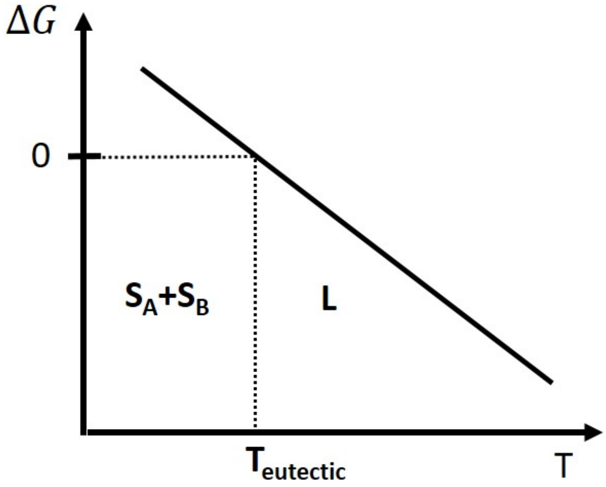

Figure 5: The change in Gibbs free energy of melting at different temperatures at eutectic composition: $T_{eutectic}$ is the melting point of the eutectic mixture, L is the liquid phase S_A and S_B is the solid phase of constituent A and B.

The change of Gibbs free energy during melting can be described as a Born-Fajans-Haber cycle of the fusion, lattice and solvation energies of the components (See Fig 6.).

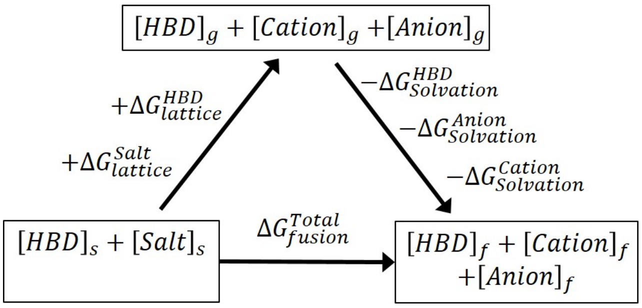

Figure 6: Born-Fajans-Haber cycle of NADES melting, lattice and solvation energies.

By that, the change of Gibbs free energy during melting:

$$\Delta G^{total}_{fusion} = \Delta G^{salt}_{lattice} + \Delta G^{HBD}_{lattice} - \Delta G^{HBD}_{solvation} - \Delta G^{Anion}_{solvation} - \Delta G^{Cation}_{solvation} \tag{3}$$

The $\Delta G_{lattice}$ contains the lattice enthalpy ($\Delta H_{lattice}$) and the entropy change of forming ionic lattice from infinitely separated gaseous ions ($\Delta S_{lattice}$):

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$$\Delta G_{lattice} = \Delta H_{lattice} - T \cdot \Delta S_{lattice} \tag{4}$$

The lattice enthalpy can be described as the function of lattice potential energy and the change in molar volume ($\Delta V_{lattice}$):

$$\Delta H_{lattice} = \Delta U_{lattice} - p \cdot \Delta V_{lattice} \tag{5}$$

We can assume that contribution of molar volume change is smaller for such less ordered, bulky compounds, what also contribute to lower melting points. When these expressions (Eq. 3-5) are implemented in the equation of the change of Gibbs free energy during melting, and isolating the eutectic temperature, we can identify the effects altering the melting point:

$$\Delta T_{eutectic} = \left[\frac{\Delta U^{salt}_{lattice} + p \cdot \Delta V^{salt} + \Delta U^{HBD}_{lattice} + p \cdot \Delta V^{HBD} - \Delta H^{HBD}_{solvation} - \Delta H^{Anion}_{solvation} - \Delta H^{Cation}_{solvation}}{\Delta S^{salt}_{lattice} + \Delta S^{HBD}_{lattice} - \Delta S^{HBD}_{solvation} - \Delta S^{Anion}_{solvation} - \Delta S^{Cation}_{solvation}}\right] \tag{6}$$

The equation implies that smaller lattice energies, stronger interactions between the constituents and a higher change in entropy during solvation results in a decrease of the melting temperature. This means that weaker crystalline structure, bulky ions and stronger interaction between the constituents yield a lower melting point. These relations are in line with the general observations. However, solving these equations requires extensive modeling to determine the lattice and solvation enthalpies, potential energies and changes in molar volume.[15]

2.2 Density, viscosity and surface tension

Most NADES have densities higher than that of water (between 1.1 and $1.4 g/cm$)[16] and significantly higher viscosities than common (organic) solvents (e.g., the viscosity of water and toluene is $0.89 mPa \cdot s$ and $0.56 mPa \cdot s$ at $25°C$, respectively, while that of the eutectic mixture of choline chloride and urea is $750 mPa \cdot s$ at $25°C$).[17] The surface tension of eutectic solvents is also larger than that of most molecular solvents and similar to imidazolium-based ILs.[2] High viscosity entails significant limitations to the mass and energy transfer during chemical reactions, therefore limiting the viscosity of NADES is necessary by selecting smaller constituent molecules with fewer hydrogen bond donating/accepting groups and weaker interaction. However, strong intermolecular forces contribute to low melting points and good solubility, which results in a trade-off between transport and solvation properties.

Density, viscosity and surface tension are mostly discussed together, as they show a similar relation to the intermolecular interaction energy and temperature (See Fig 7.). Higher interaction energy increases all three properties,[12;2;18] while higher temperature results in a decrease of these properties.[12;19;20;21] The relation of these properties to the temperature can best be described by non-linear functions, but the effect of the structure of the constituents is only vaguely described. The density showed a quadratic relationship with the temperature,[20] while the viscosity-temperature relation follows an Arrhenius equation (see Fig 7. a)) .[21] Increasing interaction between the components yields a higher density.[2] Comparing the viscosity of sugar derivatives, ethylene glycol and glycerol based NADES, viscosity shows an increase with the hydrogen bonding ability of these constituents (more hydrogen group donating group in sugars).[2] Strong hydrogen bonding seems to hinder the mobility in the NADES. The comparison of choline chloride-urea and choline chloride-ethylene glycol mixtures suggests a higher surface tension with the increasing strength of the hydrogen bonds in the first instance.[18] The disruption of the hydrogen bond network decreases all three values (e. g., the addition of a quaternary component).[12;2]

To rationalize the observed relations, the hole theory was considered.[10;22] This phenomenological model describes ionic liquids as an ensemble of particles and vacancies with variable size (See Fig 8.).[23] Its application was suggested due to the analogies between NADES and ILs. The average hole size can be calculated from experimental measurements of the surface tension, and can subsequently be used for calculation of other properties of the system. The increase of viscosity is interpreted in the model as a result of a decreased average hole diameter (due to stronger interactions). Abbot et al. studied the design of low viscosity NADES by application of this hole theory, but the model did not prove to be sufficiently accurate.[22]

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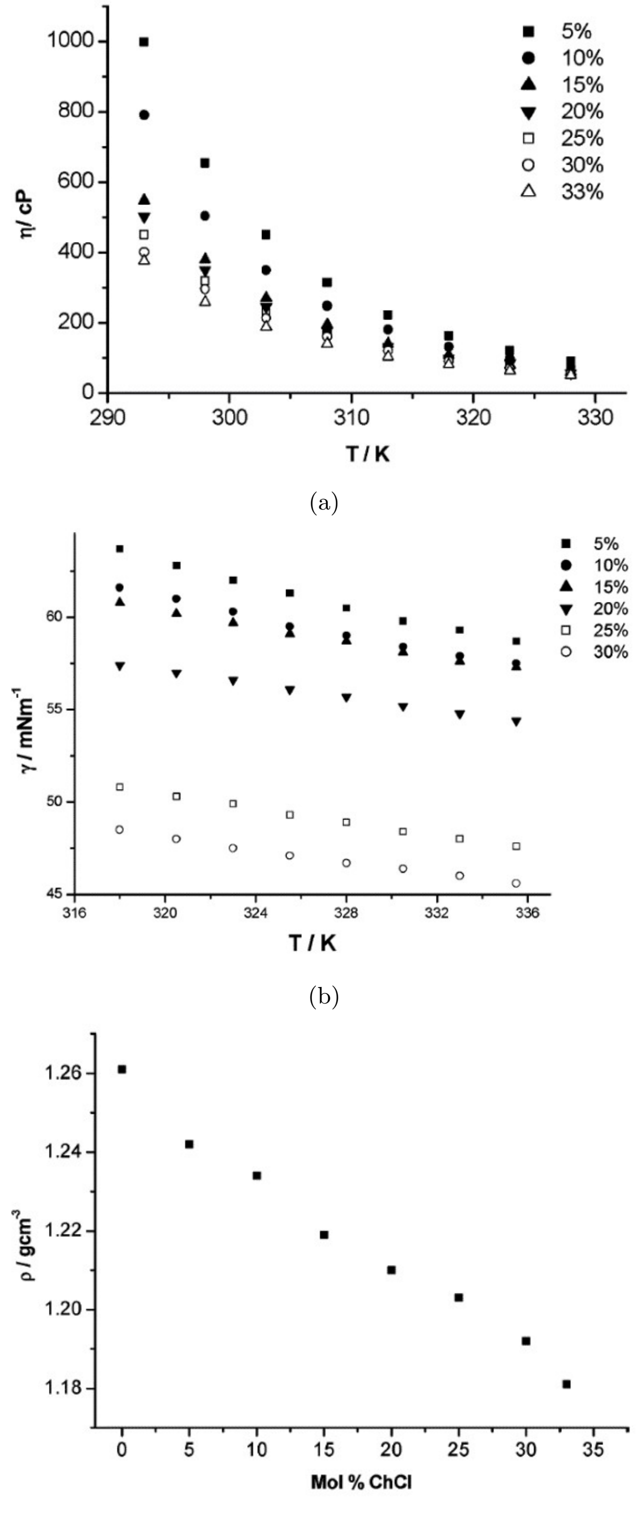

(a)

(b)

(c)

Figure 7: Relation between the composition and properties of the NADES of choline chloride - glycerol. (Taken from the work of Abbot et al.[12]) The different markings on a) and b) indicate the choline chloride ratio in the mixture (0.05-0.33 molar ratio). a) Viscosity of the NADES as function of temperature and composition, b) Surface tension of NADES as the function of temperature and composition, c) Density of the NADES as the function of composition.

2.3 Polarity, ionic conductivity and pH

The polarity, ionic conductivity and the acidity/alkalinity of NADES received little attention thus far, although these properties are relevant for many applications in electrochemistry. The polarity of choline chloride and glycerol mixtures shows similar values to $RNH_3^+X^-$, $R_2NH_2^+X^-$ and imidazolium-based ILs and it increases

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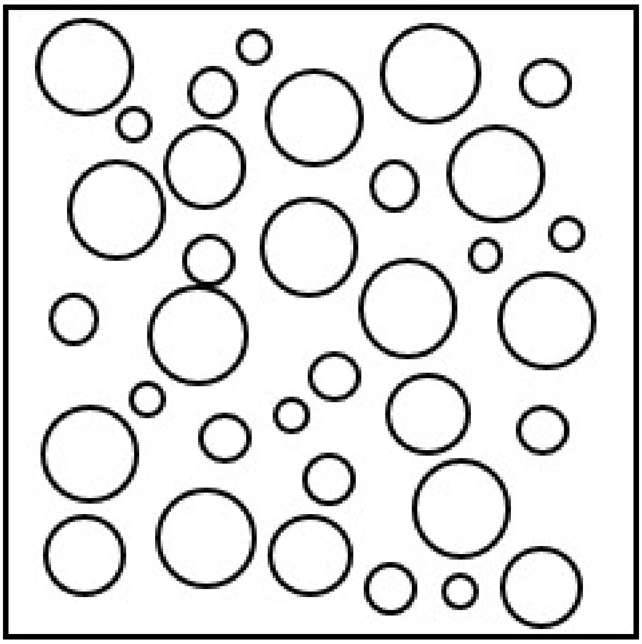

Figure 8: The hole theory with randomly located and variable-sized holes in the liquid. The model describes the structure of liquid salts, as they would have "tiny volume elements, varying in size from the subatomic to about six ions, which are empty and constantly fluctuating in size." [23]

linearly with the salt concentration. [12] Due to their high viscosities, NADES typically show poor conductivity. [12] An increase in temperature (as it decreases the viscosity) increases the conductivity. The molar ratio of constituents also affects the conductivity through its effect on the viscosity. An increased concentration of charge carrying species (salts) has a positive effect on conductivity. [13] The nature of the HBD strongly affects the acidity/alkalinity of NADES. The choline chloride-urea eutectic mixture shows weak alkalinity, [24] while sugar derived polyols as HBD yield NADES with neutral pH. [14] The alkalinity makes the absorption of acidic gases, such as CO_2, preferable.

2.4 Water content

Many NADES are susceptible to water uptake, as water can take part in the hydrogen bonding network and quaternary ammonium salts are highly hygroscopic. The incorporation of water into the hydrogen bonding system and its altering effect was demonstrated by both NMR spectroscopy [16] and molecular simulations. [25] Consequently the water content affects all of the other properties significantly. $5w/w\%$ of water absorption decreases the melting point of the choline chloride-urea mixture from $25°C$ to $15°C$, [26] while the viscosity decreased by 83%. [27] The absorbed water disrupts the interaction between the components, yielding a decrease in density and viscosity. This sensitivity calls for special care during the characterization of physicochemical properties, as the water intake during the measurements itself yields significant deviation in the results. [25] On the other hand, by controlled addition of water, the properties of NADES can be fine-tuned.

2.5 Solubility

Solvation is a complex process, as the solubility and solvation energy depend on many factors. In thermodynamic terms of view, stronger hydrogen bonding among the NADES constituents should decrease the enthalpy of the solvation and therefore increasing the dissolution, but the available information in the literature is limited.

NADES as solvent were studied mainly in three distinctive fields: the dissolution of CO_2, metal oxides and drugs. The dissolution of metal oxides in NADES for the separation and recycling of metals can be a green process in electrochemistry. Abbot et al. demonstrated first the solubility of metal oxides in NADES. [10] The solvation of the metals and metal oxides occurs via their complexation with the NADES molecules, therefore the structure of the applied constituents has a significant effect on the solubility, e.g. metal oxides with more covalent character (such as TiO_2) are poorly soluble. [2] Elevated temperature also increases the solubility. Quantum chemical simulations showed that the hydrogen network forms an open cluster and the solvation accompanied

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by proton transfer.[28]

The application of NADES for CO_2 is intensively studied. The solubility of CO_2 depends on three factors, viz. the partial pressure of CO_2, the temperature and the molar ratio of the NADES components.[29] Higher pressures and lower temperatures increase the solubility of CO_2, while the NADES with eutectic molar composition yield higher CO_2 solubility than NADES with excess of either HBA or HBD constituents. Increasing the water content has a negative effect on the solubility, since water acts as an antisolvent for CO_2 in the eutectic mixture of choline chloride and urea.[30]

As the hydrogen bonding network can form strong interactions, even with larger molecules, the solubilization of otherwise poorly soluble drugs might be done in NADES. Morrison et al. reported the increased solubility of poorly water soluble molecules in NADES and NADES/water mixtures.[31] The solubility of rutin also showed improvements in urea, sugar, organic acid and choline chloride based NADES, compared to water.[32] In latter case, the presence of basic sites in the NADES lead to an increased solubility due to the acidic properties of the rutin.[33]

2.6 Effect on enzymatic reactions

NADES provide not only green media for enzymatic reactions, but they modify the kinetic parameters and yields of reactions compared to conventional media.[7] Strong hydrogen bond donors such as urea were beforehand expected to denature proteins, but enzymes remained stable in the eutectic mixture in earlier reports. The study of Monhemi et al. showed, that the intermolecular hydrogen bonding network decreases the denaturing effect of the individual NADES constituents, by preventing the NADES constituents from diffusion into the protein chain and disrupting its secondary structure.[34]

In case of the aminolysis of ethyl valerate with lipase B from *Candida antarctica* in a choline chloride-glycerol mixture, an increase of 13 % in enzyme activity was reported, compared to toluene as solvent.[35] The choline chloride-urea mixture increased the half-life of horseradish peroxidase enzyme from 50 minutes (in phosphate buffer) up to 350 minutes.[36] The latter observation was related to the stabilization effect of the hydrogen bonding network in NADES.

The reports show that NADES may influence both the conversion and kinetics of enzymatic reactions. The thermodynamic stability of substrates and products is altered by solvation, while the viscosity affects the mass transfer of all the reactants (substrate, product, catalyst). The enzyme/NADES interaction could lead to the stabilization or denaturation of the enzyme, but also change in enzyme's active site, secondary or tertiary structure. These phenomena are the result of the hydrogen bonding interactions between the constituents of the NADES and/or the actors of the enzymatic reaction. Moreover, competing reactions of the NADES constituents with the enzyme and/or the substrates are also possible. However, the available information is highly fragmented and the relationship between these effects and the structure of NADES is still unclear, even on qualitative level. As we will discuss in the later sections, qualitative relations between the NADES structure and its effect on enzymatic reactions can be elucidated by computational methods.

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3 Modeling the properties of NADES

In the former section we reviewed the relevant physicochemical properties and phenomena of NADES, which have to be taken into account during of the solvent design for new applications. By modeling eutectic mixtures, we can better understand and even predict the behavior of these systems. As mentioned earlier, no comprehensive model of such systems was created yet. However, many different methods are available to describe certain distinct characteristics of given eutectics. While introducing these characteristics, we will proceed from the modeling of intermolecular interactions to the direction of bulk systems. First, the molecular scale models will be discussed; predominantly based on density functional theory and molecular dynamics. Thereafter we discuss macroscale models that may calculate the properties of the bulk material (solubility, density, viscosity). Lastly, we discuss methods based on large amount of experimental data, like group contribution methods and machine learning algorithms. Overall, this section focuses on the theoretical background of the methods, their field of application along with the advantages and drawbacks, case studied of actual applications and future challenges.

3.1 Molecular scale modeling

The aim in computational chemistry is to understand the properties of and the interactions in the investigated system and to apply the acquired information in the design of the system.[37] Computational methods permit observation of processes at time and length scales that are not accessible through experimental methods. Additionally, computational methods can complement experimental results, and thereby provide a deeper understanding of the system.

In both density functional theory (DFT) and classical molecular dynamics (MD), the model system is described by the interaction between the atoms (or particles) of the system, from which the distance, spatial distribution, strength of the interaction between the constituents, etc., can be determined accurately.[38] [39] However, the two methods are based on a different theoretical framework. DFT is a first principles method where the interaction energy is expressed as a functional of the electron density.[40] DFT does therefore not require empirical parameters, although it does require the application of a functional which is only an approximation to the “true” functional (e.g., the functional of exchange and correlation energies among the electrons are not known exactly, therefore approximations are used). DFT typically has a high computational intensity, which limits the system size (up to few hundred atoms). In classical MD on the other hand, the atoms interact through a (semi-)empirical force field or interaction potential.[41] While this allows the computation of much bigger systems (up to $10^7 - 10^{11}$ atoms), it does not allow the direct calculation of electronic or magnetic properties such as band gaps or magnetic moments. In MD, forces can also be obtained from first principle approaches similar to DFT (“ab initio MD”).[42] [43] Although both method are applicable for simulation of NADES, due to the high computational costs, ab initio MD is scarcely used in this application domain.

Molecular scale methods are useful for the rationalization of intermolecular interactions in NADES, which are assumed to be the main reason of their outstanding properties. As DFT and MD can obtain information at a resolution and length scale currently inaccessible to experiments, they can help the interpretation of chemical reactions in NADES, e.g. enzymatic catalysis or electrochemical treatment of surfaces. These methods may also aid in the rationalization of macroscale NADES properties. However, the direct interpretation of the results at the macroscale is limited by the size and length of the simulation, i.e., investigated attribute does not reach its equilibrium within a feasible calculation time and the correlation length of some attributes could exceed the size limitation of the model. For example, in MD simulations of NADES the calculated physicochemical properties, such as density and surface tension showed good agreement with experimental data, but the calculated transport properties had significant error. DFT calculations are also the basis of the COSMO-RS continuum model, which will be discussed later.

3.1.1 Density functional theory

DFT simulations of NADES describe the conformation of the components and the strength of interaction between them.[38] The simulation is suitable for the identification of hydrogen bonding by the method described by both Zhu et al.[8] and Zhang et al.[44] They compared the site-site distances to the related van der Waals radii of the atoms: where the distance between the sites was shorter compared with the van der Waals radius, they assumed hydrogen bonding interaction between the sites. The electrostatic potential analysis (ESP) determines the spatial distribution of electrostatic potential, which provides information about the electrostatic interactions in the system.[45] Meanwhile, reduced density gradient analysis (RDG) is also an useful tool to describe the noncovalent interactions in the system.[46] From DFT results, vibrational spectra can be calculated.[47] The

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vibrational spectra of NADES are typically difficult to evaluate due to the complex interactions, hence the computed spectra facilitate their interpretation.[48] DFT calculations can be done either on finite-size systems (a few molecules or small cluster, using localized orbitals / basis set)[49] [50] or on periodic systems (using a plane wave basis set).[51] [28] Depending on the (physical) system, and the desired representation thereof, either can be chosen. Among NADES simulations we can find examples for both cases.

Although the basic DFT functionals do not include the London dispersion forces,[52] this issue can be overcome by the application of dispersion corrected functionals.[53] These corrections are important for NADES, as they often contain alkyl side chains and aromatic moieties, therefore dispersion forces have a significant contribution to non-covalent interaction energies.[54] Also, the dispersion forces may significantly influence ionic interactions. Although this correction does not have a significant effect on the vibrational spectra (dispersion forces can be detected only in the far infrared region), in structure optimization it results in a significant difference.[8] The application of DFT simulation for gas phase molecular structures results in a good agreement between the calculated spectra and experimental results.[8] However, the simulation of NADES' physicochemical properties requires the simulation in liquid phase.

In the available literature two main application domains of DFT are distinguished; the description of molecular structures and intermolecular interactions between the NADES constituents on the one hand, and the rationalization of NADES applications by computational simulations on the other hand. Garcia et al. combined the DFT calculations with the topological analysis of the NADES electronic density.[50] By this, they set up a relation between the melting temperature and structure of the hydrogen bonding network of the NADES. The structure was described by the AIM (Atoms in Molecules) approach (Method for the topological analysis on the electronic density of the system). Others applied charge decomposition analysis (method for determination of direction and extent of charge transfer between the constituents) to correlate the strength of interactions in the system to the melting temperatures.[55] The DFT simulation of Stefanovic et al. revealed fundamentally different hydrogen bond network structures with different constituents which rationalized the significantly different melting point changes to some extent.[51] Zhu et al. used the DFT simulations to calculate the vibrational spectra of the NADES and identified the peaks of the experimental spectra.[8] Rimsza et al. studied the application of NADES in surface etching of copper.[28] The DFT simulation described the ionic character of the urea during the interaction with elemental and ionic copper. That was done by comparing the different binding energies between neutral and anionic form of urea and elemental copper and copper oxide. In another study, the simulation explained the electrochemical deposition process of magnesium metal in the mixture of choline chloride and magnesium chloride hexahydrate.[44] The most likely reactions near the cathode were determined by identifying the cationic species in the system. The CO_2 capturing ability of DES was also studied by DFT calculations: the hydrogen bonding interaction in the system was calculated before and after the addition of CO_2 to the system (new NADES-CO_2 interactions).[49]

In the future, DFT simulation will remain a key method for the investigation of molecular interactions, charge transfer and thermodynamic changes associated with the formation of NADES. Such simulations will be also useful to rationalize novel applications of NADES. The experience of simulations of IL could be a useful starting point for these studies, e.g., the process of cellulose dissolution in NADES is assumed to be similar to the dissolution in IL, which is already described in the literature. However, the size and time limitations of the method require its combined application with experimental methods or simulation of the extended system by e.g. molecular dynamics.

3.1.2 Classical molecular dynamics

MD considers either atoms or groups of atoms as the basic particles of the system; simulations are done by integrating the relevant equations of motion through discretization of time.[39] New positions, velocities and accelerations are obtained from atomic forces which are obtained as the negative gradient of some empirically derived force field.[37] As we mentioned earlier, both classical and ab initio MD simulations of NADES are feasible.[42] [43] [56] However, we only discuss works with the classical methods here as these are more common in NADES-related applications. These force fields are typically built on some functional form determined by the type of system to be studied, and then parametrized for the specific system.[57] MD methods can simulate larger systems and are able to calculate physical chemical parameters, like density or viscosity.[58] [59] MD is also applicable to study the structural characteristics of the system. This latter is done by calculating the radial distribution function (RDF) and spatial distribution function (SDF). The first describes the density function of the distance between selected particles.[60] The second is the visualization of the spatial distribution of the constituent particles around a selected molecule.[61] With these methods the hydrogen bonding interaction of the system can be studied. As the solvation dynamics are too fast to be monitored by experimental methods,

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MD simulations constitute a solid complementary method for such studies. The simulation of larger systems allows applying MD for the investigation of the microstructural properties of enzymes in NADES and rationalize experimental results.

Although MD can simulate bigger systems, the accuracy of the method depends on the applied force field and its proper parametrization.[57] As this method does not say anything about the electrons and their interaction in the system, MD is not applicable for the determination of electrical properties or for molecular structure optimization, which is required for the determination of the equilibrium structure (unlike DFT). Therefore MD calculations are often amended by DFT calculations to find the optimal molecular structures. Although, classical MD is suitable to investigate the vibrational properties of liquids through calculating the phonon spectrum, this method was not used yet for NADES simulations.[62] [63]

Similarly to DFT, the reported applications of MD mainly consider the rationalization of NADES behavior and the their practical applications (e.g., CO_2 absorption), but the simulation of macromolecular system and selection of proper force field for the calculations is also discussed. The investigation of applied force field parameters showed the significant effect of applied charge schemes regarding the calculated properties and intermolecular interactions of the system.[57] The right method for the determination of charge assignment is vital for accurate simulation. Doherty et al. developed new force field potentials for choline chloride based DES (non-polarizable force field, OPLS (Optimized Potentials for Liquid Simulations) -DES).[56] The simulations with this force field gave good agreement with the experimental results of density, viscosity, heat capacity and surface tension. However, the quantitative simulation of self-diffusion coefficients proved to be a challenge with the presented potentials. Sun et al. simulated the structural characteristics of choline chloride-urea system and determined the relation between the molar composition and interactions energies of the system.[64] The simulation also revealed a long range ordered structure among the ionic compounds of the system and yielded information about the strength and lifetime of hydrogen bonding interactions between specific sites. Another study used MD to calculate density, heat capacity and self-diffusion coefficient of the simulated system.[65] Although MD is not able to reproduce vibrational spectra, the structural and hydrogen bond analysis of the system was applied to rationalize the experimental spectrum. Das et al. combined MD simulations with steady state fluorescence emission measurement to study the relaxation dynamics, spatial and dynamic heterogeneity aspects of eutectic solvents.[66] The simulation of particle displacement during the relaxation of the system proved its homogeneity. Monhemi et al. studied the microstructural properties of a macromolecule, i.e. *Candida antarctica* lipase B in NADES.[34] The simulations described the enzyme-NADES interactions and the potential diffusion of the constituents inside the macromolecule. The comparison of these processes in water to an aqueous solution of the NADES constituents on the one hand and to the pure NADES on the other hand rationalized the stabilizing effect of NADES on macromolecules. Ullah et al. studied NADES for CO_2 capturing along with their physical chemical properties by MD simulations.[49] The method described the hydrogen bonding network in the system and its change during the absorption of CO_2. The affinity between the solvent and CO_2 was determined in the gas-liquid interfacial region to rationalize the absorption and migration of the CO_2 molecules toward the bulk fluid region.

As NADES can be used as green solvent in the field of food, feed and pharma industries, it is imperative to better understand their interaction with proteins and polymers. This also covers the application of NADES to host enzymatic reactions. As MD methods are appropriate for the modeling such systems, they may be vital in the development of these novel applications.

3.2 Macroscale modeling

We refer to macroscale modeling as all methods aiming to model NADES properties in the bulk rather via the direct intermolecular interactions among the constituents. The targeted parameters include their physicochemical properties as density, viscosity, which gives some overlapping with the earlier discussed methods, but also solvation energies and thermodynamic equilibrium properties of liquids properties, which are relevant to practical applications. Although such macroscale models still incorporate theoretical considerations, they mostly rely on input data from empirical observations or on the results of other calculation methods.

3.2.1 COSMO-RS

Conductor-like screening model for a real solvent (COSMO-RS) is a method to describe the thermodynamic properties of pure compounds and mixtures of compounds based on the unimolecular quantum chemical calculations of constituents.[67] [68] COSMO-RS combines quantum chemical calculations with statistical thermodynamic approaches to overcome the limitations of dielectric continuum solvation models (in these models the

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solvent is modelled as a polarizable continuum to descrase the computational intensity).[69] [70] Klamt gave a comprehensive overview of the model,[71] therefore we only give a short description about its working principle (See Fig. 9.). The model uses the output of quantum chemical calculations such as the charge density surface of the molecule (σ-surface). The model transforms this into discrete surface segments with an area and screening density charge. Here the contribution of hydrogen bonding, electrostatic misfit (the deviation of the electrostatic interaction energy from the idealized contact of same charges with different polarities) and van der Waals interactions are taken into account. Next, the model calculates the sigma profile: the screening density charge distribution of the molecule surface. The sigma profile of the complete system is the sum of the individual sigma profiles weighted with the molar ratio of the compounds. The chemical potential is calculated by an iterative function of the sigma profile of the system. This chemical potential is the basis for the computation of other thermodynamic properties. The model calculates the thermodynamic properties of liquid mixtures including solubility, partition coefficient and the liquid-liquid equilibria.

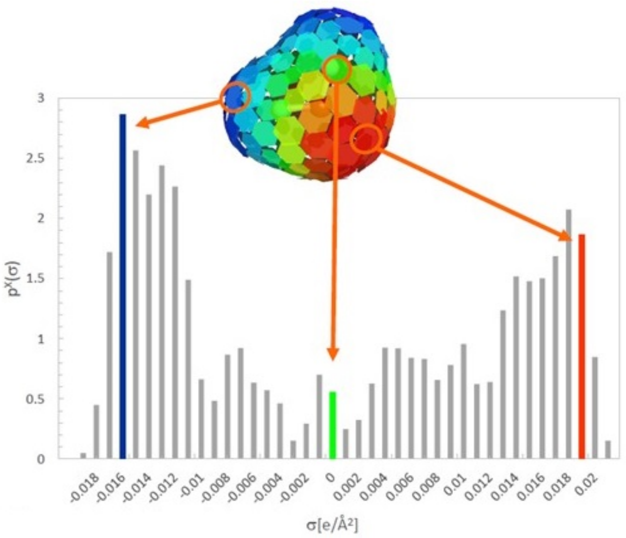

Figure 9: Determination of sigma profile of water based on the results of DFT simulation. (Taken from COSMO-RS theory, The Basics.[72])

Since the method does not need experimental data of the studied system, it is appropriate for preliminary screening and rationalization of structural characteristics (i.e., the probability distribution of charge density can be used for the interpretation of molecular interactions). The drawback of this technique is the unknown composition and dissociation state of the investigated ionic compounds (when such are present), which has to be determined separately. Although the simplicity of the model's algorithm makes its application easy, the necessity of preliminary quantum chemical calculations could be a difficulty for novel compounds.

COSMO-RS was primarily applied in screening of DES for applications where the liquid-liquid equilibria are relevant (i.e. liquid-liquid separation, chromatography). Mulyono et al. investigated the liquid-liquid extraction of BTEX aromatics from n-octane by using DES.[73] They used COSMO-RS to predict the ternary liquid-liquid equilibria diagram of the studied systems, where the method showed only qualitative agreement with the experimental results. Also the calculated sigma profiles were used to describe the interactions between the DES and the solute compounds. Another research screened DES for use in extractive denitrification of diesel.[74] The activity coefficient of nitrogen compounds in DES was predicted and it was used for the calculation of selectivity, capacity and performance index of the DES. Based on the results, they also set up assumptions regarding the relations of the strength of interaction to the structure of the compounds. However, due to the lack of experimental validation of these results, it is possible that the screened liquid eutectic systems do not exist in reality. Gouveia et al. also tested DES for the separation of aromatic and aliphatic hydrocarbons via liquid-liquid extraction.[75] They used COSMO-RS to predict the phase behavior and tie lines of the ternary mixtures with small relative error. The method was also able to describe the trend of distribution ratio and selectivity of different DES. A different research group used the COSMO-RS to predict the interaction mechanism between the constituents of DES.[76] They compared the sigma profiles of the pure constituents and the formed DES. They also found good agreement between the predicted and experimental density. Bezold et al. assessed the application of COSMO-RS in model for the calculation of thermodynamic properties of DES in liquid-liquid chromatography.[77] They found qualitative agreement between the activity coefficients, liquid-liquid equilibria data and partition coefficients taken from experimental measurements and literature data. They found the

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overall prediction quality to be sufficient for pre-screening procedure in solvent system selection. Jeliński et al. used the COSMO-RS methodology for the screening of DES for the solvation of rutin by predicting the solubility.[33] Their applied model also took into consideration the possible ionic and neutral form of the HBA. They used their findings to describe relation between the structural properties of the NADES and the solubility values. Finally, COSMO-RS was also used as a screening tool to predict the thermodynamic properties of sugar based, ternary DES.[78] The comparison of predicted and measured eutectic point showed good agreement.

Due to its capabilities, COSMO-RS will remain a valuable method for pre-screening tasks in the future for applications related to the liquid equilibria properties of NADES and their solutes. However, the experimental validation of the results cannot be omitted, as the predictions thus far often yielded only qualitative agreement with the actual results. This also raises the question, to which extent can the results of the calculations (without experimental validation) be used in the investigation of the general structure-property relation of NADES.

3.2.2 PC-SAFT

Perturbed-Chain Statistical Association Fluid Theory (PC-SAFT) is an advanced equation of state model.[79] PC-SAFT is a thermodynamic model for phase equilibrium calculations: it describes the relation between energy, volume, pressure, temperature and composition in the fluid region. It is also an association model, which means it also describes the effects of hydrogen bonding between the compounds of the system.[80] To calculate the total energy of the hydrogen bonding, the model uses a perturbation theory: they approximate the solution of a complex problem with the solution of a simpler problem, then they use perturbation parts to incorporate the differences.[81] [82] The detailed theoretical background of the method can be found elsewhere,[83] here we give only a short description of the main considerations. In this model molecules of a reference fluid are constituted by the addition of equal sized spherical segments into a hard chain. (See Fig. 10.) The total interaction energy is expressed as the sum energy of the ideal gas system and the residual energy of the interactions (See Eq. 7.). The residual energy contains the contribution of the interaction in the hard-chain reference, the dispersion interactions among the chains and the specific site-site hydrogen bonding interactions in the system. (See Eq. 8.) The equation is usually expressed in Helmholtz free energy as most thermodynamic properties can be obtained by its differentiation.

$$a^{total} = a^{ideal} + a^{residual} \tag{7}$$

$$a^{residual} = a^{hard-chain} a^{dispersion} + a^{association} \tag{8}$$

Each compound in the model requires characterization by five pure component parameters: the number of segments, the diameter of segments, energy of the segment, volume of association and energy of association. Empirical binary interaction parameters can be also added to the model. This increases the accuracy of the model by incorporating the interactions among the constituent and solutes. These parameters have to be determined experimentally by regression on the vapour pressure and liquid density data of the pure components or by group contribution methods (if available).

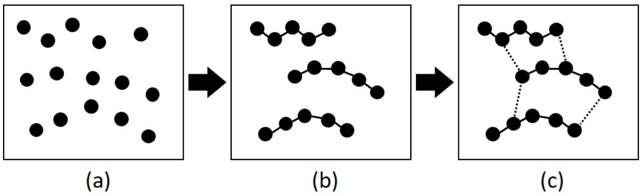

Figure 10: Schematic representation of PC-SAFT theory: the equal-sized spherical segments (a) connected by covalent bonds, forming the hard-chain reference fluid. (b) The specific interactions among the chains are described by the perturbation parts. (c)

The accurate prediction of the thermodynamic properties is the main advantage of the method. The calculated behaviour of vapour-liquid, liquid-liquid and solid-liquid phase equilibria show quantitative agreement with the experimental results in many cases. Therefore solubility, separation properties, gas absorption (e.g., CO_2) and the melting point can be predicted by this method. More complex properties can be determined by coupling PC-SAFT with additional models, where the calculated thermodynamic properties are the input for further steps (see work of Haghbaksh et al. in the next paragraph). On the other hand, the determination of

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the pure component parameters can be difficult. Their determination based on experimental dataset requires a significant amount of extra work. The pure component parameters of NADES raises another question: the mixture of the compounds can be described as one pseudo-pure component or individually. The second approach yields a more general model, but the determination of individual parameters is not always feasible. In case of NADES, where solid constituents are applied, the determination of vapour pressure and liquid density data is not feasible. To overcome this issue, the parameters can be determined from the aqueous solutions of the constituents, however that is not feasible in case of hydrophobic constituents.

Similar to COSMO-RS, PC-SAFT can also be used for solubility calculations. Verevkin et al. applied PC-SAFT to calculate the limiting activity coefficients of aliphatic and aromatic organic compounds in DES.[84] The comparison of calculated and experimental values showed agreement at the order of magnitude. Moreover, the predicted temperature dependency followed the trend of experimental results. Gas absorption capabilities can be investigated by the determination of liquid-vapor equilibria. Zubier et al. applied a PC-SAFT model to investigate CO_2 capture in DES.[85] They determined the phase behavior of the eutectic systems with CO_2. They applied both of the above-mentioned strategies for the determination of pure component parameters. Although both strategies yielded accurate predictions on phase behavior, the individual-component approach yielded more versatile parameters: with pseudo-pure approach not just the pure component parameters were DES-specific (as they were determined for given DES), but also the binary interaction parameters became ratio specific. An additional research group investigated the CO_2 solubility of DES with constituents, that were hydrophobic and solid at room temperature, therefore they could only use pseudo-pure parameters for their calculations.[86] Still, the calculations predicted CO_2 solubility with reasonable accuracy, even without the application of binary interaction parameters. PC-SAFT is also useful for the determination of the melting point in eutectic systems. Pontes et al. applied PC-SAFT to describe the solid-liquid phase diagrams of 15 quaternary ammonium and fatty acid based DES.[87] Based on the experimental results they connected the increasing chain length with increasing molecular interaction and lower melting point as consequence. They incorporated that effect in the binary interaction parameter of the thermodynamic modeling. The predicted melting point showed good agreement with the experimental data (around 7K average absolute deviation). As we mentioned earlier the PC-SAFT can be coupled with additional models. Haghbaksh et al. combined PC-SAFT and Cubic plus Association models with free volume theory to create a predictive viscosity model for DES. The equation of state models provided the density of the system, which is a required parameter for the viscosity calculations by the free volume theory.[88] The viscosity calculation with PC-SAFT yielded accurate predictions (with 2.7% average deviation). In their second work, they combined the same equation of state models with the frictional theory to build an additional viscosity model.[88] Here PC-SAFT was used to determine the repulsive and attractive pressure values, which are the input parameters of the frictional theory. The final model showed reasonable predictive accuracy with 4.4% average deviation.

PC-SAFT has a future potential in the determination of thermodynamic properties of the NADES systems. As more and more data become available about eutectic systems, the pure component parameter determination will become easier, making the method application more straightforward. The coupling of the equation with additional models on both input and output side is still a relatively unexploited area, where the initial results are promising.

3.3 Group contribution and machine learning methods

The methods we discuss in this section focus on the description of the structure-property relationship in DES systems.[89] It is common in the group contribution and machine learning methods, that the aim is not the general understanding anymore, but rather the quantitative prediction of the systems properties. To achieve this, these methods use large datasets to describe the relation between the structural properties and the behavior of the investigated systems.[90] Rather than theoretical considerations, these methods work with empirical models relying on heavy parametrization. In case of machine learning black box models are often used, were the model does not yield minimal information about the rationale of the described relation.[91] The quantitative agreement between the predicted and experimental data can be achieved, however the amount of required data is often the bottleneck of such methods.[92]

3.3.1 Group contribution methods

Group contribution methods calculate the properties of chemical compounds based on their structure.[93] In principle the method assigns contributions of the groups to a given property, that describes how the chemical compound is built. The property of the whole compound is the added contributions of the consisting groups.

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By that, large number of different compounds can be characterized with the small amount of information on the group contributions. The application of such contribution method reduces the required data and computational intensity of the calculations. Still, the determination of the group contributions require a large experimental dataset (e.g., Hansen et al. applied around 1200 datapoint for their software to predict the Hansen solubility parameters[94]). One common example is the Lydersen-Joback-Reid method, where the thermodynamic properties of the chemicals is determined based on their structural composition.[95]

The main advantage of group contribution methods is the simplicity of the calculations, which only require the structure as input. The method can yield quantitative accuracy, multiple physicochemical properties were determined with an average error lower than 5.0%.[19] [96;97;98] On the other hand quality of the estimation depends on the limitations of the method itself and the structural domain covered. The development of the contribution dataset is also labour intensive, but available system can be enhanced subsequently.[99]

For the determination of solvation properties, Hansen solubility parameters are usually determined through group contribution methods (e.g., Hoftyzer and van Krevelen method).[99] However, their implementation for NADES due to the special hydrogen bonding interactions and the presence of ionic compounds is not straightforward. Still, Lee et al. used the group contribution methods of van Krevelen of Hansen solubility parameters to predict the melting point decrease of DES.[100] They take into account the difference in polar and hydrogen bonding parameters of the HBD component to compose the regression model of melting point depression of choline chloride based DES. The regression model gave 0.738 as coefficient of determination. The other frequently used method for DES is the earlier mentioned Lydersen-Joback-Reid group contribution, usually coupled with other calculations where the group contribution gives the input values. Shahbaz et al. developed a predictive model for the density of DES.[101] They used the Modified Lydersen-Joback-Reid method for the determination of the critical properties of molecules.[95] They combined the results with Lee-Kesler mixing rules and the modified Rackett equation to calculate the liquid density. The error of the predicted densities was 1.9%. In their other study, they used the same method for the evaluation of additional DES and to compare the method to artificial neural network based estimations.[19] The group contribution based method yielded a 2.03% error in that case. Shahbaz et al. also used the group contribution method of Knotts et al. for the prediction of parachor values of DES.[97] The parachor value links the surface tension, density and structure of the compound and they used the group contribution method for the determination of surface tension and density. Additionally, they combined the results with the Othmer equation to describe the temperature dependency of the surface tension of the investigated DES. The experimental and predicted surface tension and density values showed good agreement with 6.4% and 1.61% average error, respectively. The predicted temperature dependency of the surface tension also gave good correlation with 2.57% average error. The method of Wildman and Crippen for the prediction of refractive indices was the third method investigated for the prediction of DES behavior.[98] They calculated the molar refraction values, and then they used the Lorentz-Lorenz equation for the determination of refractive indices and the density. The error of the refractive indices were 0.56%, while it was 1.43% in the case of density calculations. Mjalli et al. compared the Modified Lydersen-Joback-Reid group contribution and Eötvos method for the calculation of critical temperatures of DES systems and the application of these for the prediction of density and surface tension values of the DESs. For the latter, they combined the Rackett and Guggenheim empirical equations. As the Eötvos and Guggenheim methods based on the experimental values of density and surface tension, it gave better results than group contribution method, especially in the higher temperature range. Finally, Mirza et al. used the combination of modified Lydersen-Joback-Reid group contribution method with the Lee-Kesler mixing rules to determine the critical properties of a large number of DES.[96] For validation, they used the Rackett-equation to calculate densities and compare with experimental values. The average deviation of the density values was 4.9%. However, the DESs containing aromatic groups had a bigger deviation, probably due to the stronger interaction force sin the system.

The main issue with the currently applied group contribution methods is that they were not developed for eutectic systems, therefore they do not take into account the special interactions of such systems. With the increase of available data on eutectics, group contribution methods directly for NADES can be developed. These specific systems would be useful for DES–based application development, due to their simplicity and predictive accuracy.

3.3.2 Machine learning methods

Machine learning is the process of computer systems performing specific tasks based on patterns and inference instead of explicit instructions.[102] In the description of structure-property relations this usually means a supervised learning task: the machine is a mathematical function, an algorithm that maps the relation between the output variable and the possible input variables.[103] Training datasets with known input-output pairs are

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used for the development. After this step, the trained algorithm can be evaluated and preferably used for the determination of the unknown output values of novel cases. In case of DES the main method used is artificial neural networks.[104] A neural network (see Fig. 11.) is made up of neurons. Neurons are some non-linear functions (e.g., sigmoid, binary, hyperbolic tangent) that sums up the values of the different input signals (from other neurons or input variables). The neurons are connected to each other and mainly aggregated into layers. The inputs are the signals from the input variables or the output of other neurons. The connections between neurons have weights adjusting the strength of the input signal. The learning process is based on the adjustment of these weights during the training.

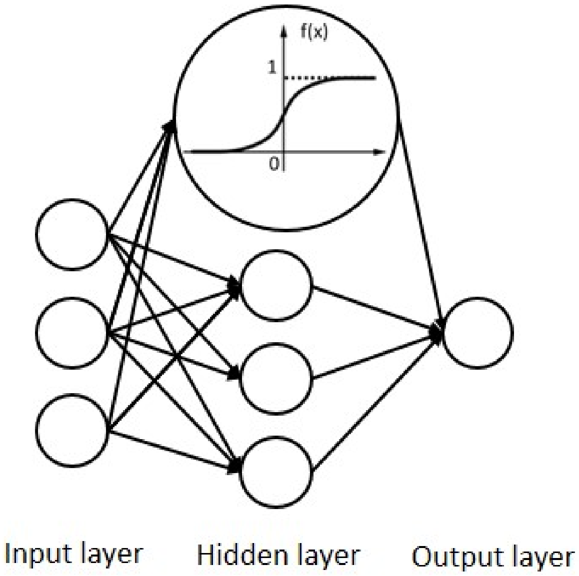

Figure 11: Artificial neural network with one hidden layer, three input variables and one outcome, The four nodes in the hidden layer use sigmoid functions for signal processing, one of the commonly applied non-linear function in neural networks.

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If proper datasets are available machine learning methods can yield good quantitative accuracy, even in the case of complex relations. On the other hand, the quality and the size of the available dataset is vital for accurate models. During the training process, the applied training data will determine to what extent of structural variability will be covered and what precision is possible. By applying a model for vastly different compounds than it was trained for, it becomes less accurate. The intention of machine learning is primarily the prediction of properties. Therefore the final model is often hard to interpret regarding the underlying structural relations (black box model).

Despite its potential, studies published on machine learning with NADES are scarce up to date. Shahbaz et al. used machine-learning methods to predict the density of different DES system based on their composition and the temperature.[19] They used a feed forward backpropagation neural network and compared its efficiency to the earlier discussed group contribution method. The method had a 0.14% error and resulted in better predictions especially at higher temperatures compared to group contribution methods. Bagh et al. used a similar feed forward backpropagation neural network to predict the electrical conductivity of DES based on the temperature and the molar composition.[105] The predicted values showed good correlation with the experimental results with a regression coefficient of 0.9988. Adeyemi et al. used both feed forward backpropagation neural networks and bagging neural networks to predict the density and conductivity of multiple amine based DES systems.[106] The bagging method yielded a significant increase in the prediction quality of these properties with $2.799 \cdot 10^{-7}$ and $5.820 \cdot 10^{-4}$ values of normalized mean square of errors in case of density and conductivity, respectively.

Similarly to group contribution methods, as more and more data become available on DES, more complex machine learning methods will be possible for modeling different properties of such systems. On the other hand, good quality data is imperative for proper model development. In our experience, composing high-quality datasets based on literature is challenging to date.

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4 Summary and outlook

Compared to common organic solvents and ionic liquids, the application of NADES may offer an economic and ecological alternative due to the cheap constituents, efficient synthesis, low toxicity and volatility. The possibility to design NADES properties through the structure of the constituents and their molar ratio in the mixture means both potential and challenge. Their application as designer solvent requires a good understanding of the structure-property relationships of these systems.

The earlier studies on the physical chemical properties of NADES showed that these are strongly related to the strength of hydrogen bonding in the system. Therefore changes of properties such as density, viscosity, surface tension or phase equilibria can be qualitatively described by the changes of the hydrogen bonding's strength. The strength of the hydrogen bonding changes with the structure of the components and their molar ratio. In the first case the number of hydrogen bond donor and acceptor sites on the molecule are determinative, but also the size and the electron affinity has effect as other intermolecular interactions are significant. The molar ratio is relevant with respect to the number of hydrogen bonds between the constituents: in the eutectic composition the ratio facilitates the maximal hydrogen bonding interaction between the constituents, leading to maximal interaction energy. This results minimal melting point, but also maximal viscosity in the eutectic point. However, the quantitative description of the structure-property relationship requires in depth modeling of these phenomena.

We discussed the models of DES in three separate sections. The molecular scale covers models based on density functional theories and molecular dynamics based methods, where the primary goal is to describe the steric configuration of the molecules in the eutectic system and the actual interaction energies between the constituents. These methods help rationalizing the behavior of DES and also the feasibility of biocatalytic reactions in strongly hygroscopic environment. In macroscale modeling the aim is to describe the properties of the bulk solution, based on semi-empirical methods instead of the actual intermolecular background. The two main methods were COSMO-RS and PC-SAFT. Both are applicable for the determination of equilibria phase properties. The third section discussed empirical models based on a large amount of data. Group contribution and machine learning models can yield quantitative precision, but their application requires large amount of experimental data.

In the following figure (Fig. 12.) we compared the different aspects of the investigated methods. While the molecular and macroscale methods can aid the interpretation of the already experienced phenomena, the macroscale, group contribution and machine learning models can predict the outcome of novel cases. While the macroscale methods yield mostly qualitative results, with group contribution and machine learning methods one can acquire quantitative predictions. The published studies determined the vibrational spectra, density, viscosity and diffusion properties with the aid of molecular scale properties. With macroscale models the phase equilibria properties like liquid-liquid, solid-liquid and vapour-liquid equilibria and solubility were calculated. Group contribution and machine learning methods predicted the density, viscosity, surface tension, electric conductivity and refractive indices different NADES systems.

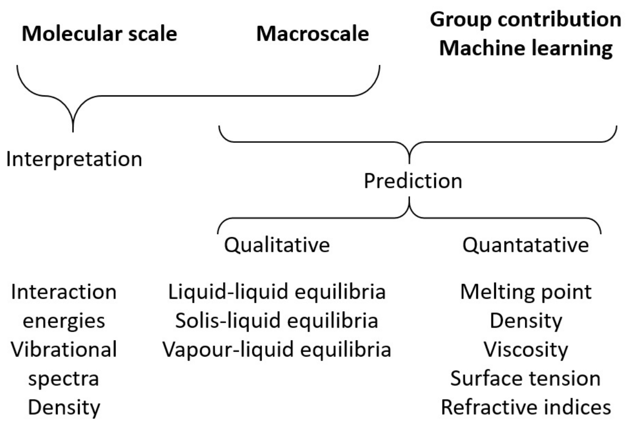

Figure 12: Different methods and their capabilities for modeling DES.

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We see the connection of different methods and the field of machine learning has the greatest potential in the future. Especially if we take into account the challenges in the field of modeling the behavior of macromolecular and biological systems in NADES. Although the combination of available methods gives a good coverage on different properties and size scale, a versatile unified methodology is yet to be developed for general, application based prediction. This calls for the combination of already available methodologies and the construction of a coherent, versatile database on the properties of NADES. A QSPR related modeling would yield the most versatile methodology for general application.

In reviewing the available literature, we identified multiple areas yet to be investigated. Due to their similarities, many modeling methods could be implemented from the modeling of ionic liquids. However, not all available methods were utilized yet, e.g., the MD simulation of macro- and biomolecules solvation. As NADES show great potential in applications regarding macro- and biomolecular systems, such as cellulose, proteins or enzymes, modeling the interactions between such compounds and the NADES should be studied in more details in the future. The collection of more and more data about eutectic systems makes possible the building of large databases, containing the physicochemical and other properties of NADES. The analysis of such databases with machine learning or other methods will facilitate the development of both descriptive and predictive models, even for more complex relations of the eutectics. The combinations of different methods, exemplified by the group contribution methods also have a great potential to describe more complex phenomena, e.g., the holistic elucidation and prediction of enzyme reactions in eutectic solvents.

Acknowledgement
This research was funded by UAntwerp BOF-STIMPRO 36493

Keywords:
Computational chemistry · Sustainable Chemistry · Solvent effects · Deep eutectic solvents · Natural deep eutectic solvents · Green solvents

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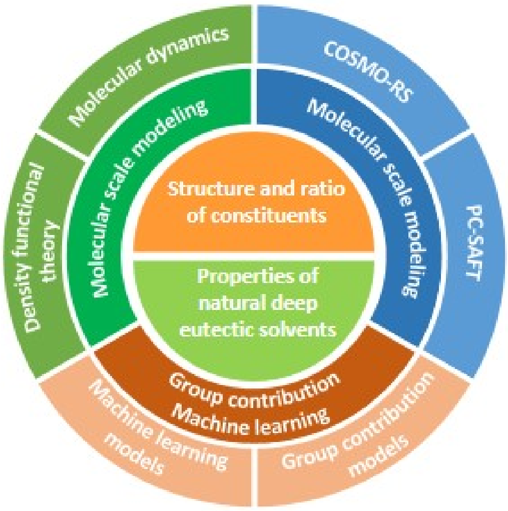

Role models: Modeling different properties of deep eutectic solvents helps to understand and predict the behavior of these novel solvents. In this review we give a summary on the available methods of modeling, review what properties can be calculated and forecast what development can be expected in the future.

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