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Insights into the Nature of Eutectic and Deep Eutectic Mixtures

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Abstract

A stricter definition of a deep eutectic solvent (DES) is urgent, so that it may become a sound basis for further developments in this field. This communication aims at contributing to deepening the understanding of eutectic and deep eutectic mixtures concerning their definition, thermodynamic nature and modelling. The glut of literature on DES applications should be followed by a similar effort to address the fundamental questions on their nature. This hopefully would contribute to correct some widespread misconceptions, and help to establish a stringent definition of what a DES is. DES are eutectic mixtures for which the eutectic point temperature should be lower to that of an ideal liquid mixture. To identify and characterize them, their phase diagrams should be known, in order to compare the real temperature depression to that predicted if ideality is assumed, and to define composition ranges for which they are in the liquid state at operating temperatures. It is also shown that hydrogen bonding between the DES components should not be used to define or characterize a DES, since this would describe many ideal mixtures. The future of deep eutectic solvents is quite promising, and we expect that this work will contribute to the efficient design and selection of the best DES for a given application, and to model properties and phase equilibria without which the process design is impractical.

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1 Introduction

The term *eutectic*, from Greek ευτηκτος, easy (or lowest) melting [1], was first used by the British physicist Frederick Guthrie in 1884 to describe "a lower temperature of liquefaction than that given by any other proportion" [2]. The description has evolved and nowadays the term eutectic reaction is defined as an isothermal reversible reaction of a liquid phase which is then transformed into two (or more) different solid phases during the cooling of a system. The eutectic point is an isobaric invariant of the system, and represents the composition and the minimum melting temperature along the two intersecting melting curves [1]. Assuming pure solid phase and neglecting the temperature influence on the heat capacities, classical thermodynamics proposes Eq. 1 to describe these melting curves,

$$\ln(x_i\gamma_i) = \frac{\Delta_{\mathrm{m}}H}{R}\left(\frac{1}{T_{\mathrm{m}}} - \frac{1}{T}\right) + \frac{\Delta_{\mathrm{m}}C_p}{R}\left(\frac{T_{\mathrm{m}}}{T} - \ln\frac{T_{\mathrm{m}}}{T} - 1\right) \tag{1}$$

where γ_i is activity coefficient of compound i at a certain liquid mole fraction composition x_i, T is the absolute temperature, T_{m} and $\Delta_{\mathrm{m}}H$ are the melting temperature and enthalpy of the pure compound, respectively, R is the universal gas constant, and $\Delta_{\mathrm{m}}C_p$ is the difference between the molar heat capacity of compound i in the liquid and solid phases. In particular, when the equilibrium temperature is not far from the melting temperature of the pure compound, the last term of the equation has a negligible value when compared to melting enthalpy term and thus, can be neglected [3, 4]. However, this specific aspect will also get some attention in this study.

Eutectic mixtures present interesting properties and have been widely applied due to the liquefaction and enhanced solubility provided by the decrease of the melting point of the mixture when compared to those of the starting pure constituents [5–7]. Examples comprise mainly active pharmaceutical ingredients and salts, due to the pharmaceutical [5] and molten salts [8] applications, respectively.

In 2003, Abbott et al. [9] coined for the first time the term 'deep eutectic solvents (DES)' to describe mixtures of amides with quaternary ammonium salts that had melting points much lower than those of their pure compounds, allegedly due to the formation of a hydrogen bonding complex between a hydrogen bond donor (HBD) and a hydrogen bond acceptor (HBA) at a well-defined stoichiometric proportion. Later, the term was extended by Abbott and co-workers to other mixtures, presenting in a review in 2014 [10] a definition stating that DES are systems formed from a eutectic mixture of Lewis or Brønsted acids and bases which can contain a variety of anionic and/or cationic species. Deep eutectic solvents were reported to be easy to prepare, widely available, nonreactive with water and versatile. They have been proposed as a cheap and greener alternative to ionic liquids and the concept became, meanwhile, widely used with more than one thousand references today in ISI Web of Science. A number of reviews on DES and their applications are available nowadays [10–13] where different definitions of what a DES is can be found.

Due to the absence of a strict and clear definition of what a 'deep eutectic solvent' is, this term is often abused. This problem is probably related to the limited number of works devoted to understanding the DES nature and what is their difference from conventional eutectic mixtures. The applications of these solvents have been the target of most works published so far. The thermodynamic characterization, namely information about their solid–liquid phase diagrams and an understanding of their interactions in the liquid phase, essential for the efficient design and selection of the best DES for a given application,

remains poorly studied, while the melting properties of their pure constituents are in many cases unknown.

2 DES Definition

The first aspect that urgently needs to be addressed is the definition of what is a DES. This must start by addressing and redressing some widespread misconceptions: DES are neither novel compounds nor pseudo pure compounds, but mixtures. Fancy commercial-like designations for these mixtures such as reline, glyceline, ethaline, and a growing number of other similar designations, should be avoided since they induce the suggestion of dealing with a new pure component. They should not be looked as low cost ILs, since they do not present the same character: DES, unlike ILs, are mixtures and not pure compounds, and can be at the best a solution of ions and not a fluid constituted solely by ionic species. DES should not be generally described as green, environmental friendly, non-toxic, easy to formulate or economic, since these characteristics depend on the starting materials used and their mixture. Many of these overgeneralizations were abused in the studies of ionic liquids and are being again used acritically in the DES literature. The existence of a eutectic point on a mixture cannot be used to define a DES—essentially all mixtures of compounds that are completely or partly immiscible in the solid phase present a eutectic point. DES are often described as hydrogen bond complexes but the presence of a hydrogen bond between two components of a mixture cannot be a sufficient condition to define a DES because an ideal mixture of hydrogen bonding compounds, e.g. mixtures of fatty acids or alcohols, must not be defined as a DES. It is also questionable if solutions of salts or any other type of hydrogen bonding compound in solvents that are liquid at ambient temperature, e.g. water, alcohols, ethylene glycol, glycerine, among others, should be considered a DES. Although it may be tempting to define aqueous solutions of salts, or other compounds as DES, as recently proposed [14], unless a clear definition of DES that clearly establishes a novel condition or behaviour of these solutions, not covered by the present definitions, it is difficult to understand why the well-established concept of solution should on these cases be now replaced by the concept of DES. On the other hand, it may be arbitrary to use a necessary condition for the definition of DES that both compounds are solid at room temperature as the definition of eutectic point does not impose any restriction of this type.

For a 'deep eutectic solvent' to be significantly different from any other eutectic mixture, and to grant any meaning to the 'deep' qualificative, a 'deep eutectic solvent' should be defined as a mixture of pure compounds for which the eutectic point temperature is below that of an ideal liquid mixture. The temperature depression should be defined as the difference (ΔT_2) between the ideal ($T_{E,ideal}$) and the real (T_E) eutectic point and not as the difference (ΔT_1) between the linear combination of the melting points of the pure components and the real eutectic point [10], see Fig. 1. This second approach seems inappropriate since, as discussed above, the presence of a eutectic point in the solid–liquid equilibria (SLE) phase diagram is a characteristic of all mixtures of compounds that are fully, or partly, immiscible in the solid phase. If ΔT_1 is used as definition of a DES then it would cover essentially any mixture of compounds, with exception of those presenting complete solid solutions or forming stable intermediate compounds with melting points comparable to those of the pure precursors. The advantage of a definition based on ΔT_2 is that it is more restrictive, grants the 'deep' qualificative, and is more sound theoretically, allowing one to draw direct relationships with the

Fig. 1 Schematic representation of the comparison of the SLE of a simple ideal eutectic mixture (red line) and a deep eutectic mixture (blue line) (Color figure online)
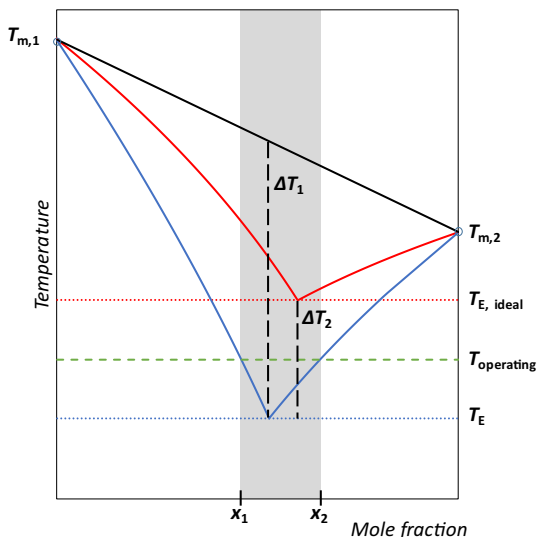
non-ideality of the liquid phase, and thus comparisons between the relative intensities of the various interactions present on a mixture HBA + HBD (viz. HBA–HBA, HBD–HBD and HBA–HBD) required to understand the non-ideality of the liquid phase that is often analyzed based solely on the strength of the HBA–HBD interactions. A good example of this partial analysis that prevents a full understanding of the system is the otherwise remarkable work by Hunt and co-workers [15] on the interactions present on a [Ch]Cl + urea mixture, essentially dismissing the notion of a dominant 2:1 HBD:HBA complex as being the basis of the DES nature. Although in many situations a direct comparison with the ideal mixture behavior may be prevented by the lack of enthalpy of fusion data, other approaches to establish the non-ideality of the liquid phase are often possible, at least for one of the compounds of the mixture.

The other relevant aspect of the definition of a DES, beside its temperature depression, is its composition. Although Abbott et al. [9] used in the definition of the [Ch]Cl + urea a fixed stoichiometric proportion of 1:2, identified as the eutectic point of the system, they also tried to establish the solid–liquid phase diagram of many of their systems [8, 9, 16, 17], both to identify the liquid phase region and the stoichiometry of the eutectic mixture. Contrarily, most other authors failed to do that and it quickly became a widely adopted practice to test mixtures with defined stoichiometric proportions of HBD and HBA (3:1, 2:1, 1:1, 1:2, 1:3 being the most used, but other intermediate or more extreme proportions are also common). This is based on a wrong notion that the eutectic point composition is directly connected to the formation of a complex, currently often found in literature the argument that a eutectic composition close to a fixed stoichiometric proportion is proof of complex formation. The eutectic composition results from the intersection of two melting curves [1] that are dominated by the fusion properties, more than the interactions between the HBD:HBA, and thus no stoichiometric meaning can be attributed to the eutectic composition, that can assume any value depending on a complex interplay between the fusion properties and the deviations to the ideality expressed by the activity coefficient, as given by Eq. 1. If no special significance can be attributed to the eutectic point composition, then the inference

that a complex is formed with a given stoichiometric proportion because the eutectic point is close to a mole fraction of 0.25, 0.33, 0.5, 0.66, 0.75, or any other, is obviously unsound.

On the other hand, given that the goal is to define a solvent that is liquid at the operating temperature of the system or process, there seems to be no reason to be focused on the eutectic composition. Any mixture with a certain composition that is in the liquid state at that temperature could be used and defined as a DES. This means that any mixture with compositions comprised between x_1 and x_2 on Fig. 1 should be considered a DES, relaxing the fixed stoichiometric proportions that have been used to characterize a DES, and instead assuming the full nature of a DES as a mixture and not just as a fixed composition complex. This has a major advantage of bringing an extra degree of freedom to the DES definition and enhancing the tunability of the DES properties that are no longer restricted to those of the eutectic point composition only. Since their structures and properties can be adjusted by selecting the right combination of the precursors, further tailoring their phase behaviour and physical properties by fine tuning their composition enhances the designer solvent character of DES [12].

In our view a 'deep eutectic solvent' is a mixture of two or more pure compounds for which the eutectic point temperature is below that of an ideal liquid mixture, presenting significant negative deviations from ideality ($\Delta T_2 > 0$). Additionally, the temperature depression should be such that the mixture is liquid at operating the temperature for a certain composition range. Otherwise, a simpler term 'eutectic solvent' could be used to describe mixtures that do not fulfill these criteria.

Based on the new proposed definition, to properly label a eutectic mixture as simple, or deep, the SLE phase diagram must be available, and the melting properties of the pure compounds must be known in order to draw the ideal solubility curve. Concerning these two aspects, in the following sections we explore the results over a series of different mixtures and compounds as well as modeling approaches helping to better establish the eutectic coordinates and the liquid phase non-idealities [18, 19].

3 SLE Phase Diagrams

The number of works that report the SLE phase diagrams of deep eutectic solvents is very limited, and attempts at modeling these data using excess Gibbs energy models (g^E) or equations of state (EoS) are even scarcer. Furthermore, several pure compounds often used in the DES formulation, like choline chloride, are not thermally characterized since they degrade upon melting. With so little information available it may not be easy to decide whether a mixture is, or is not, a DES, based on the definition proposed above. For that reason the DES label has been often used based solely on the physical state of the mixtures at room temperature, neglecting the fact that this mixture can be just an ideal liquid mixture without any deviation from the ideal solubility curve—i.e., a simple eutectic mixture. In the next sections, solid–liquid phase diagrams for mixtures reported as DES in the literature, involving different classes of compounds, will be analyzed and discussed in order to contribute to a better understanding of the nature of the liquid phase of these mixtures, in particular in what concerns to their liquid phase non-ideality.

3.1 Terpene-Based Mixtures

The formation of eutectic mixtures between active pharmaceutical ingredients (APIs) and excipients have long been studied for the development of new drugs or drug formulations [5]. If the decrease of the melting point of the pure components (without the formation of a new compound) is an advantage in increasing solubility and bioavaliability, it can also lead to the undesirable melting of a tablet powder. Terpenes are a class of natural compounds widely used in the pharmaceutical field and their interactions with drugs have been extensively evaluated since well before the advent of DES. Mixtures of borneol/menthol [20–22], and camphor/menthol [23, 24], were proposed as vehicles for transdermal delivery [5] while mixtures of thymol with ibuprofen [25] or meloxicam [26] and of menthol with ibuprofen [7, 25, 27], testosterone [28], lidocaine [29], or ubiquinone [30] have been investigated as analgesic, antimicrobial and anti-inflammatory vehicles. Under the new DES perspective menthol-based eutectic mixtures with pyruvic, acetic, L-lactic and lauric acids were reported as hydrophobic, low viscosity, DES, and applied to the extraction of caffeine, tryptophan, isophthalic acid, and vanillin [31]. Moreover mixtures of menthol and ibuprofen [32], benzoic acid, acetylsalicylic acid or phenylacetic acid [33] were called therapeutic deep eutectic solvents and used to design a controlled drug delivery system and as dissolution enhancers of active pharmaceutical ingredients. The mixture of menthol and lauric acid was also proposed as a hydrophobic DES and was applied to extract indium from aqueous solutions with low acidity [34]. Other mixtures of DL-menthol with caprylic, capric and lauric acids were also proposed as hydrophobic DES and used to extract neonicotinoids from diluted aqueous solutions [35]. Duarte et al. [36] proposed a DES composed of menthol and three different APIs: ibuprofen, BA, and phenylacetic acid, and demonstrated their efficiency in the enhancement of the solubility, permeability and thus, bioavailability of APIs by changing the physical state of the pure components. From another perspective, menthol:flurbiprofen was suggested as a DES to avoid menthol crystallization and allow the estimation of its glass transition temperature [37]. Later, Dietz et al. [38] selectively separated furfural and hydroxymethylfurfural from an aqueous solution using supported so-called DES (decanoic acid and thymol or menthol, and thymol and lidocaine) liquid membranes. Finally, the polarity of DES mixtures of DL-menthol and acetic, levulinic, octanoic and dodecanoic acids was evaluated through solvatochromic responses of UV–vis absorption probes [39]. Unlike previous pharma oriented works, the recent publications under the DES concept fail to study the SLE phase diagram, focusing essentially on the application.

Figure 2 shows some examples of SLE phase diagrams involving terpenes and APIs that can be found in the open literature. The solubility curves of terpenes thymol and menthol are almost ideal in all cases displayed. The ibuprofen solubility curve presents negative deviations to ideality while testosterone seems to have an ideal behavior, with the exception of two points close to the eutectic point.

3.1.1 Are Ideal Liquid Mixtures DES?

Given the interest that terpene based DES has been attracting [13, 16, 33], we recently characterized eutectic mixtures composed of the terpenes L(−)-menthol and thymol and carboxylic acids caprylic, capric, lauric, myristic, palmitic and stearic. The SLE phase diagrams were measured, compared with the predictions assuming an ideal
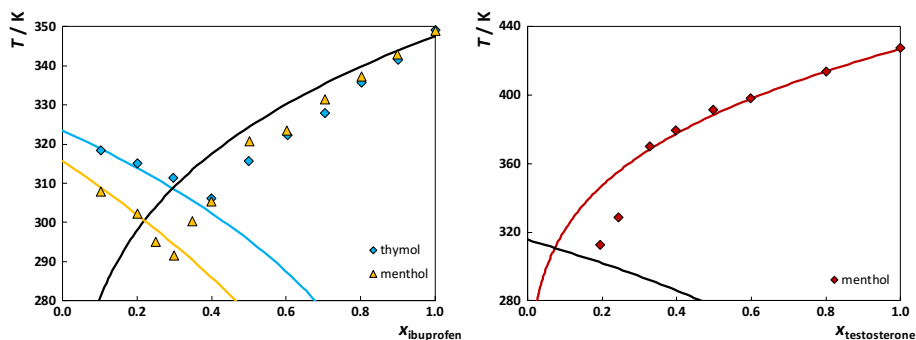
Fig. 2 Solid–liquid phase diagrams of mixtures composed of terpenes and APIs. Symbols represent experimental data [25, 28] while lines represent the ideal solubility curves

liquid phase, and correlated using the Perturbed Chain-Statistical Associating Fluid Theory (PC-SAFT) equation of state [40]. The thermal properties of the pure components used in the preparation of these DES are well established in the literature and thus it was possible to calculate, without any ambiguity, the ideal solubility curves using Eq. 1, considering the activity coefficient equal to one. Figure 3 shows the experimental SLE diagrams of two of the mixtures investigated together with the ideal solubility curves and the PC-SAFT modelling results. The experimental SLE phase diagrams and the eutectic point were successfully described using both the ideality and the PC-SAFT EoS. Both approaches show that, in spite of being labelled as DES in the literature, these systems present a quasi-ideal behavior with small deviations from ideality, and a eutectic point close to that predicted assuming an ideal liquid phase. This means that the interactions between the two components are not significantly different from those present in the pure compounds, to induce negative deviations from ideality, and the temperature depressions associated to them. Yet, in many cases, in spite of presenting an ideal behavior, the eutectic mixture is liquid at room temperature, while both pure components are solid. Moreover, the results shown in Fig. 3c clearly establish that there is not a stoichiometric relationship between the two compounds at the eutectic point, but that the eutectic composition is well correlated to the melting properties of the carboxylic acids. As already pointed out this must not be seen as a limitation as it reinforces the tunable character of the eutectic point of these mixtures, emphasizing the need of measuring their phase diagrams for proper applications.

3.2 Choline Based DES

The HBA most widely used in DES formulations are quaternary ammonium salts, particularly choline chloride, [Ch]Cl, due to its low cost, non-toxicity, biodegradability and economic synthesis. This organic compound is mass-produced and used as an additive to accelerate growth in the poultry industry. DES formed by [Ch]Cl [8, 9, 41, 42] have been proposed as green solvents for a wide range of applications [10, 11, 13], but the application of the DES definition proposed above to these mixtures faces one problem: the [Ch]Cl melting properties are not available. The decomposition of pure [Ch]Cl before/upon melting [43] precludes the direct measurement of its melting properties. Given the importance

Fig. 3 Solid–liquid phase diagrams of mixtures composed of lauric acid and terpenes **a** L(−)-menthol and **b** thymol. Symbols represent experimental data measured by us (unpublished data) while lines represent the modelling results: red dashed line, ideal; thick line, PC-SAFT; dotted line, T_E predicted by PC-SAFT. Gray regions represent the concentration range for which the mixture is liquid at room temperature ($T = 298.15$ K). **c** Eutectic compositions, predicted by PC-SAFT, of the different mixtures composed by terpenes and fatty acids as a function of the melting temperature of the acid (T_m ranking order: caprylic < capric < lauric < palmitic < myristic < stearic) (Color figure online)
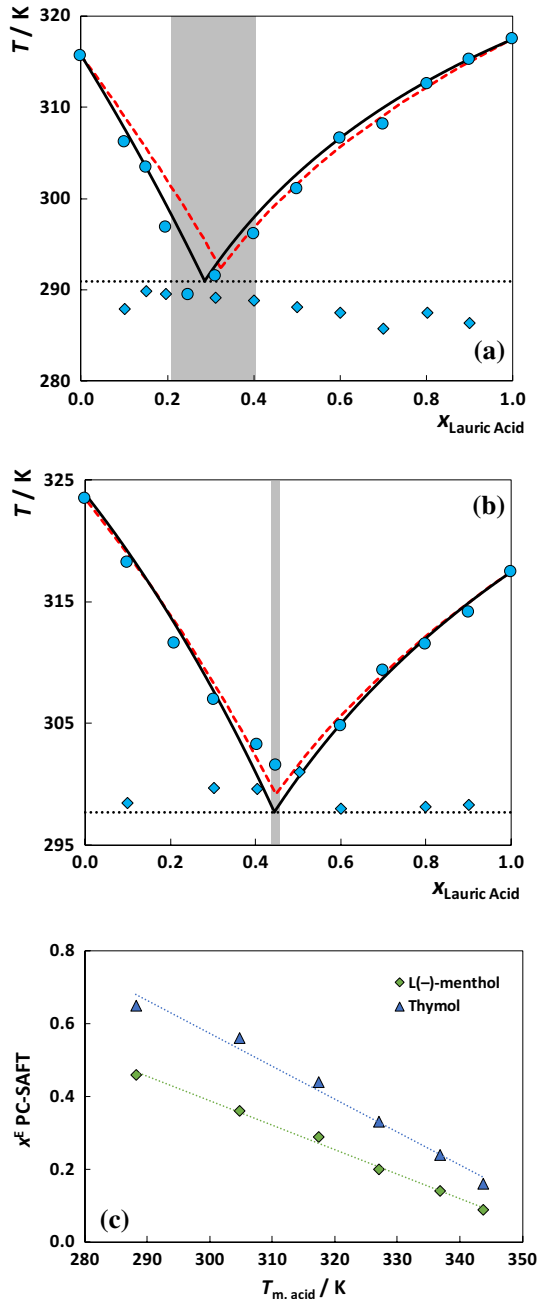
of choline-based DES we must find a way to try to establish, even if only approximately, the melting properties of [Ch]Cl necessary to thermodynamically characterize the choline-based eutectic systems and to describe their SLE.

3.2.1 [Ch]Cl Melting Properties

Since the decomposition prevents, or at least strongly hinders, the use of direct techniques for the measurement of choline chloride melting enthalpy and temperature, a work based on an indirect approach to estimate the fusion properties of [Ch]Cl was proposed by us [44]. Based on the quasi-ideal behavior of the liquid phase of mixtures of ionic liquids [45, 46], the solubility curves of ten different ionic compounds with choline chloride forming simple binary eutectic mixtures were measured and the fusion properties of [Ch]Cl estimated by linear regression of the SLE, Eq. 1, being obtained $T_{m,[Ch]Cl} = 597 \pm 7$ K and $\Delta_m H_{[Ch]Cl} = 4300 \pm 600$ J·mol^{-1} [44]. For this estimation, the difference between the specific heats of the solid and liquid phases was neglected since these values were not available, and their estimation was not possible with the available information. This introduces a relevant uncertainty on the fusion enthalpy leading to a value that could be significantly underestimated. However, this estimated melting enthalpy has the same order of magnitude if compared to the few equivalent, and still uncertain, data measured by DSC for other molten salts containing the same cation: [Ch][NTf$_2$] (4680 J·mol^{-1} [47], 1226.5 J·mol^{-1} [44]); [Ch][CH$_3$SO$_3$] (5100 J·mol^{-1} [48]); [Ch][Ac] (16,500 J·mol^{-1} [49]); [Ch][Prop] (2238.6 J·mol^{-1} [44]); [Ch][Buta] (8793.6 J·mol^{-1} [44]).

When the temperature range of the system is not far from the melting temperature of the pure compound the representation of SLE using Eq. 1 without the heat capacity term is widely accepted and successful [3, 50, 51]. However, that is not generally the scenario when searching for the solubility of pharmaceuticals, phenolic compounds or other organic molecules in pure water, or organic solvents, nor in the case of choline chloride systems where the melting temperature of choline is close to 600 K while the eutectic point is in some cases near to room temperature. Naturally, the validity of this assumption depends on the relative magnitude of that property and the enthalpy of melting.

Looking into the particular case of choline chloride, some simple calculations were carried out (Fig. S1 of Supporting Information) at the estimated melting temperature of 597 K. In these figures we present the magnitude of the enthalpy term as percentage of the total. What is remarkable is that even for a heat capacity change as low as 10 J·mol^{-1}·K^{-1} a significant impact of that term is observed in the results when the enthalpy of melting is low, at least at temperatures close to room temperature. It is then advisable to evaluate the impact of neglecting the heat capacity change in the numerical values of the estimated enthalpy.

Several studies have been carried out to estimate the heat capacity change upon melting, mainly for common organic compounds, but also for substances such as ibuprofen, naproxen or mannitol [44, 52–56]. Besides the group-contribution and molecular descriptors methods, which are not possible to apply to choline chloride due to the absence of the groups or parameters to describe it, there is an interesting, simple, and attractive approach proposed by Hildebrand et al. [56], who suggested approximating the heat capacity change to the entropy of melting ($\Delta_m S$). With such an assumption Eq. 1 becomes:

$$\ln(x_i \gamma_i) = \frac{\Delta_m H}{R T_m} \ln \frac{T}{T_m} \qquad (2)$$

Using exactly the same data as in Ref. [44], assuming also ideality, from the linearity between $\ln x_i$ and $\ln(T/T_m)$ (Fig. S2) an estimation for the heat capacity change can be found: $\Delta_m C_p = \Delta_m H / T_m = 8.71 \pm 0.45$ J·mol^{-1}·K^{-1}, which is equivalent to $\Delta_m H_{[Ch]Cl} = 5202 \pm 597$ J·mol^{-1}. These values are pretty close to those published previously

[44], but in that work a much better fit and correlation was found. In fact, in the vast majority of cases that approximation for the heat capacity change seems to overestimate the value, and it has been shown that the real value is somewhere between $0.5\Delta_m S$ and $\Delta_m S$ [44, 52], meaning that neglecting the heat capacity term in Eq. 1 is, for this compound, very acceptable.

The usefulness and robustness of the estimated fusion properties of choline chloride, and additional studies on the influence of it $\Delta_m C_p$ is now evaluated more extensively. The mixture choline chloride + urea was chosen as the model system and its solid–liquid phase diagram measured and compared with values from the literature [9, 57, 58]—see Fig. 4.

As can be seen, the experimental values are rather scattered with different authors presenting eutectic temperatures ranging from approximately 285 to 300.6 K. This is probably due to the water content of the samples since the mixture choline chloride + urea is highly hygroscopic. Meng et al. [58] performed a detailed study regarding the impact of water on the melting temperature of this system. They also attribute the discrepancies observed between the various authors to the presence of water. They found that after 2 days, samples absorbed around 5.5 wt% of water leading to a decrease of 15 °C in the melting temperature. This calls for improvements in the physicochemical characterization of eutectic and deep eutectic mixtures. Compounds and/or their mixtures should be properly dried and a proper quantification of their water content must be systematically performed before any physicochemical measurement.

Besides the experimental data on the SLE phase diagram, Fig. 4 presents the ideal solubility curve of urea that can be easily calculated since its fusion properties are well established ($T_{m,urea} = 407.2$ K and $\Delta_m H_{urea} = 14.6$ kJ·mol^{-1}). It shows, as expected for this archetypal DES, a significant negative deviation from ideality, suggesting that the interactions urea–[Ch]Cl are significantly stronger that those of urea–urea. The figure presents also various possible representations for the solubility curve of choline chloride. These were calculated using $T_{m,[Ch]Cl} = 597$ K [44] and adopting various values of $0 < \Delta_m C_p < 20$ J·mol^{-1}·K^{-1}, with $\Delta_m H$ fitted to the solubility data of the ten quasi-ideal
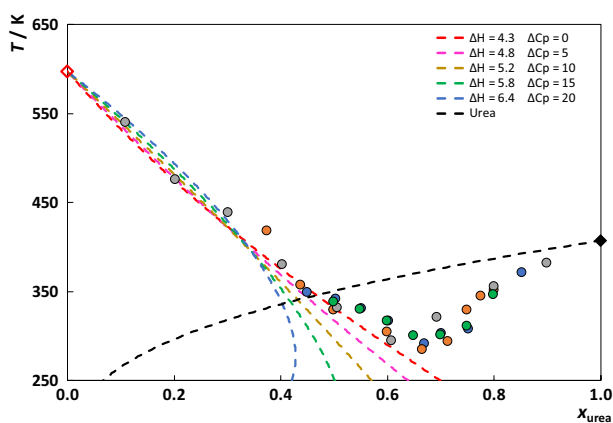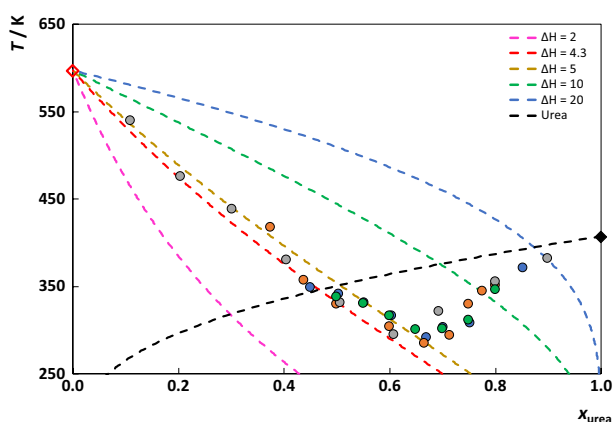

Fig. 4 Solid–liquid phase diagram of mixtures composed of choline chloride and urea. Full symbols represent experimental data: filled diamond, [59]; blue circle, [57]; orange circle, [9]; green circle, [58]; grey circle, unpublished data and the open diamond symbol, stands for the estimated $T_{m,[Ch]Cl} = 597$ K [44]. Dotted lines correspond to ideal solubility curves calculated through Eq. 1 with $T_{m,[Ch]Cl} = 597$ K [44]. $\Delta_m H$ and $\Delta_m C_p$ are presented in units of kJ·mol^{-1} and J·mol^{-1}·K^{-1}, respectively (Color figure online)

systems measured in our previous work [44]. The increase of the value of $\Delta_m C_p$ leads to a corresponding increase in the melting enthalpy. While a $\Delta_m C_p = 0$ suggests that the [Ch]Cl has an surprisingly ideal behavior in the liquid phase with urea, the use of higher, and more realistic, values for the $\Delta_m C_p$ with the corresponding higher melting enthalpies lead to a downshift of the calculated ideal solubility curves implying that the [Ch]Cl will probably show a positive deviation to ideality on the DES mixture, which is very counterintuitive. For values of $\Delta_m C_p \geq 20$ J·mol^{-1}·K^{-1} the ideal solubility curve starts to present weird and unsound physical behavior as shown in Fig. 4. This suggests that the strong decrease in the melting points of the [Ch]Cl + urea mixtures is mainly due to the peculiar fusion properties of [Ch]Cl and not to a HBD:HBA complex formation as commonly proposed, and to the negative deviations from ideality of urea, as established by Araujo et al. [60], rather than of [Ch]Cl as is widely accepted.

In an alternative analysis, fixing $\Delta_m C_p = 0$, $T_{m,[Ch]Cl} = 597$ J·mol^{-1} [44] and varying the melting enthalpy of choline chloride, Fig. 5, it is possible to see the impact of this property on the slope of the ideal solubility curve of [Ch]Cl. It is clear from these results that the strong decrease of the melting point curve can be more easily justified by a low fusion enthalpy than by a strong negative deviation from ideality, since it shifts considerably the eutectic composition and temperature to values much higher than those observed experimentally. In Fig. S3, it is possible to find a similar analysis, by changing the value of $\Delta_m C_p$ to 5, 10, 20, 25 and 50 J·mol^{-1}·K^{-1}, and observing the corresponding melting enthalpy values that can describe satisfactorily the experimental data. Once again, a low melting enthalpy is favorable up to 20 J·mol^{-1}·K^{-1}, indicating that for higher heat capacity changes upon melting there is no possibility of describing the experimental data unless a strongly temperature-dependent non-ideality plays a role.

The system choline chloride + urea is extremely interesting due to the negative deviations from ideality in the urea solubility curve and to the almost ideal behavior, or with a weak positive deviation from ideality in the choline chloride solubility curve. We hope that in the future flash DSC can, from calorimetric measurements, provide direct information on the melting properties of [Ch]Cl, helping to validate hypothesis of ideality

Fig. 5 Solid–liquid phase diagram of mixtures composed of choline chloride and urea. Full symbols represent experimental data: filled diamond, [59]; blue circle, [57]; orange circle, [9]; green circle, [58]; grey circle, unpublished data, and the empty diamond symbol, stands for the estimated $T_{m,[Ch]Cl} = 597$ K [44]. Dotted lines correspond to ideal solubility curves calculated through Eq. 1 with $T_{m,[Ch]Cl} = 597$ K [44] and $\Delta_m C_p = 0$ J·mol^{-1}·K^{-1}. $\Delta_m H$ is presented in units of kJ·mol^{-1} (Color figure online)

assumed so far and enabling a proper modelling of this and other systems, either with equations of state or excess Gibbs models, for a full description of their properties.

3.2.2 Assessing the Liquid Phase Non-ideality of [Ch]Cl-Based DES

As mentioned above, [Ch]Cl is the most widely used HBA to prepare DES. We have been conducting a systematic study of SLE phase diagrams of mixtures reported on the literature as DES based on [Ch]Cl. For a thermodynamic characterization of the liquid phase, the knowledge of the melting properties of choline chloride, even if determined indirectly, and with some uncertainty associated to the value of $\Delta_m C_p$, are essential for the systems characterization and the development of models to describe the phase behavior. Ultimately, this approach should lead to the possibility of designing new DES using computer aided molecular design approaches, instead of the trial and error method used nowadays.

3.2.3 Choline Chloride + Fatty Alcohols/Acids

The SLE diagrams of eight systems formed by choline chloride and fatty alcohols or fatty acids were reported by us [19]. Two examples are shown in Fig. 6. The ideal solubility curves of [Ch]Cl were calculated using $T_{m,[Ch]Cl} = 597$ K [44] and with different values of $\Delta_m C_p$ and $\Delta_m H$ that were estimated from Eq. 1 and the solubility data of the ten quasi-ideal systems reported previously [44]. PC-SAFT and NRTL (non-random two-liquid) models were used to correlate these systems, and both provide a good description of the experimental data, with PC-SAFT being more accurate, especially for the systems presenting higher deviations from ideality [19].

Assuming the melting properties reported by Fernandez et al. [17], it can be seen in Fig. 6 that all systems investigated present quasi-ideal behavior with eutectic temperatures very close to those predicted assuming an ideal liquid phase ($\Delta T_2 \approx 0$, Fig. 1). If higher values for the $\Delta_m C_p$ of [Ch]Cl are used, then a shift of the ideal melting lines to lower
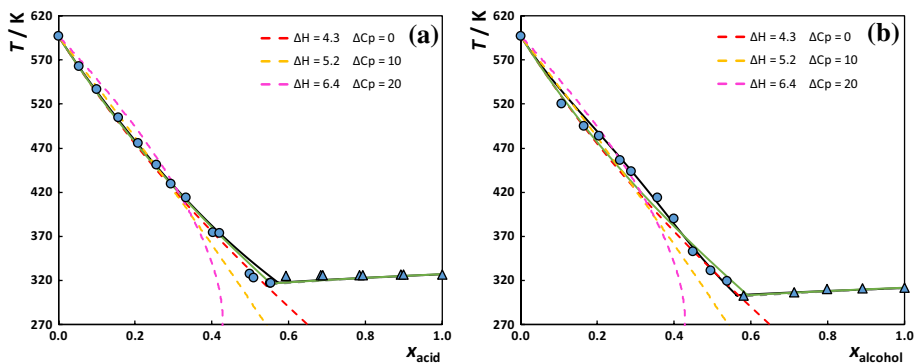
Fig. 6 SLE phase diagrams for the binary mixtures composed of [Ch]Cl and: **a** myristic acid and **b** 1-tetradecanol. Symbols represent experimental data measured [19] while solid lines represent modeling results: black line, PC-SAFT; green line, NRTL. Dashed lines represent the ideal solubility curves ($T_{m,[Ch]Cl} = 597$ K [44]; $T_{m,myristic\ acid} = 327.03$ K and $\Delta_m H_{myristic\ acid} = 45.75$ kJ·mol^{-1}, $T_{m,1\text{-tetradecanol}} = 311.72$ K and $\Delta_m H_{1\text{-tetradecanol}} = 45.81$ kJ·mol^{-1}). $\Delta_m H$ and $\Delta_m C_p$ of [Ch]Cl are presented in units of kJ·mol^{-1} and J·mol^{-1}·K^{-1}, respectively (Color figure online)

temperatures is observed, indicating the presence of positive deviations from ideality for [Ch]Cl. The picture that emerges is thus that the fatty acids and fatty alcohols studied are not able to form HBA:HBD interactions stronger than those present in the pure compounds, and for [Ch]Cl probably these are even weaker. These mixtures must then be considered simple eutectic mixtures and not DES.

3.2.4 Natural Deep Eutectic Solvents (NADESs)

There is a subgroup of DES formed by naturally occurring compounds, such as organic acids, amino acids, sugars and sugar alcohols that have been labeled in the literature as natural deep eutectic solvents (NADESs) [13, 41, 61–67]. This is a fairly meaningless designation, used more to market some DES mixtures, since it could be argued that most DES based not only on choline, but many other HBA, including the archetypical [Ch]Cl:urea will fall onto this category. Similarly it could be argued that since [Ch]Cl is industrially produced from HCl, ethylene oxide and trimethyl amine there is little natural about it. Despite their very high viscosities, these DES have been investigated for applications in food, cosmetic, agrochemical and pharmaceutical industries, usually in the presence of water [61, 68, 69].

Industrially there is an important application of NADES that has been implemented, and is being used to obtain the plant extracts commercialized by the trademark of Eutectys™ by Naturex. This new set of botanical extracts is based on the patented extraction process named by the authors as eutectigenesis [70]. This consists of extracting active compounds of plants through the formation of NADES. This eco-extraction technology offers a natural alternative to conventional solvents and makes it possible to capture precious metabolites from the plant [71]. Due to the nature of the compounds used as extraction solvents, the extracts may remain contaminated with DES after extraction, which become part of the final formulation.

The number of works reporting data on the solid–liquid equilibria of NADES is as expected extremely low [13, 62, 72, 73], most probably due to the poor thermal stability of the pure components involved [74]. To overcome this lack of data, the SLE of six binary mixtures involving choline chloride and sugars, and the ternary systems [Ch]Cl + D-mannose + D(+)-xylose and [Ch]Cl + D-glucose + D(−)-fructose, were measured by us and the

Fig. 7 SLE phase diagrams for the binary mixtures composed of [Ch]Cl and: blue circle, sucrose; red circle, D-glucose; yellow circle, D-mannose (unpublished data). Lines represent the ideal solubility curves calculated through Eq. 1 with $T_{m,[Ch]Cl} = 597$ K [44]. $\Delta_m H$ and $\Delta_m C_p$ are presented in units of kJ·mol^{-1} and J.mol^{-1}·K^{-1}, respectively (Color figure online)
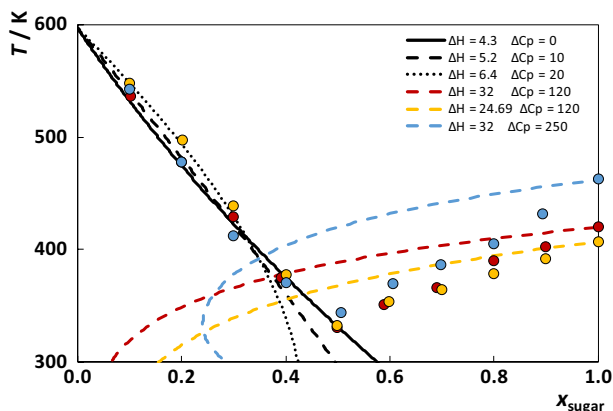
data used to evaluate the nature of these systems. Figure 7 displays three examples of the SLE curves measured experimentally along with the ideal solubility lines, these last calculated using melting properties found in the literature [75–79].

These systems are characterized by a single-eutectic point close to the equimolar composition, at a temperature lower than the one predicted ideally and at a significantly different composition. Although, as discussed for other systems above, choline chloride presents a quasi-ideal behavior in the liquid phase, or positive deviations if $\Delta_m C_{p[Ch]Cl} \neq 0$ is considered, while sugars show strong negative deviations to ideality suggesting the presence of strong favorable interactions between them and [Ch]Cl.

Although the eutectic temperature is significantly below those predicted by the ideal liquid mixture ($\Delta T_2 > 0$), obeying the condition needed to be a DES, the melting temperatures of these mixtures are well above room temperature, in stark contradiction to what is often reported in the literature [62, 80] where these DES are said to be liquid at room temperature. To evaluate the reasons behind this apparent contradiction the effect of the water content on the melting points of these systems was studied. These data were submitted for publication during the preparation of the current manuscript. It was shown that 3 wt% of water was enough for the eutectic point of [Ch]Cl + D-mannose to become liquid at room temperature, while [Ch]Cl + D(+)-xylose required 9 wt% of water. In general quantities of water less than 10 wt%, that given the hygroscopicity of [Ch]Cl can be easily drawn from atmosphere, are enough to bring the melting points of [Ch]Cl + sugar mixtures to values close to, or below, room temperature, with the additional advantage to densities and viscosities, which are significantly decreased. However, one must recall that 3 wt% of water on these systems corresponds to 35 mol%, while 10 wt% to 65 mol%. From a thermodynamic point of view we are no longer in presence of a DES with some humidity but in presence of aqueous solutions of a sugar + [Ch]Cl.
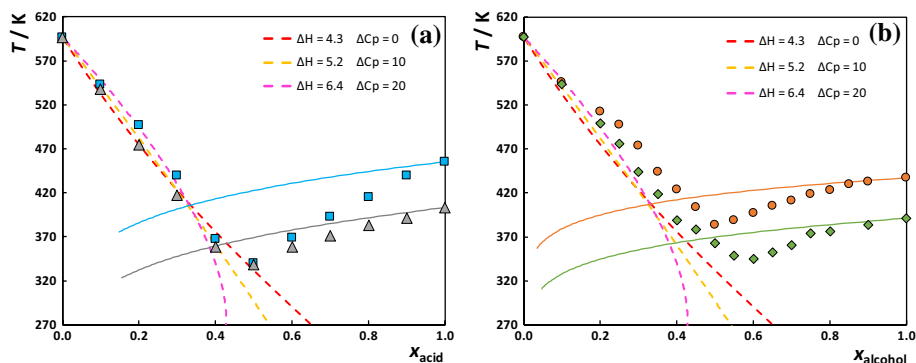
Fig. 8 Solid–liquid phase diagrams of mixtures of choline chloride and: blue square, succinic acid; grey triangle, malic acid; orange circle, mannitol; green diamond, meso-erythritol. Symbols represent the experimental data (unpublished data) while solid lines represent the ideal solubility curves ($T_{m,[Ch]Cl} = 597$ K [44]; $T_{m,succinic\ acid} = 455.20$ K and $\Delta_m H_{succinic\ acid} = 34$ kJ·mol^{-1} [81]; $T_{m,malic\ acid} = 403.15$ K and $\Delta_m H_{malic\ acid} = 25.3$ kJ·mol^{-1} [82]; $T_{m,mannitol} = 437.30$ K and $\Delta_m H_{mannitol} = 54.69$ kJ·mol^{-1} [83]; $T_{m,meso-erythritol} = 391.20$ K and $\Delta_m H_{meso-erythritol} = 38.9$ kJ·mol^{-1} [84]). $\Delta_m H$ and $\Delta_m C_p$ of [Ch]Cl are presented in kJ·mol^{-1} and J·mol^{-1}·K^{-1}, respectively (Color figure online)

3.2.5 Choline Chloride + Sugar Alcohols/Polycarboxylic Acids

Other mixtures between choline chloride and sugar alcohols or polycarboxylic acids were studied and their experimental SLE phase diagrams measured—Fig. 8. The ideal solubility lines were calculated as mentioned above. The polycarboxylic acids tested, present an almost ideal behavior on the solubility curve of choline chloride and negative deviations to ideality on the acid curve. When the HBDs are sugar alcohols there are negative deviations from ideality in the alcohol solubility curve and positive deviations in the choline chloride solubility curve.

3.3 DES Based on Other Quaternary Ammonium HBA

Due to the remarkable performance of choline chloride in the deep eutectic formulations and their applications, other quaternary ammonium chlorides have been explored by several authors [18, 34, 85–87]. In this context and following the efforts to characterize the SLE of eutectic and deep eutectic mixtures, the phase diagrams of fifteen new mixtures composed of quaternary ammonium salts (tetramethylammonium chloride, $[N_{1111}]Cl$; tetraethylammonium chloride, $[N_{2222}]Cl$; and tetrapropylammonium chloride, $[N_{3333}]Cl$) and fatty acids (capric, lauric, myristic, palmitic or stearic acids) were measured and modelled with the PC-SAFT EoS [18]. Due to their vast natural sources, fatty acids have a very positive impact in the mixtures formulation and in the process sustainability. Figure 9 shows the SLE and the activity coefficients of lauric acid and $[N_{1111}]$ Cl or $[N_{2222}]Cl$ or $[N_{3333}]Cl$ [18], compared with the results presented before involving [Ch]Cl [19]. PC-SAFT was found to be a useful tool in the description of the SLE of these systems and to give reliable estimations of the eutectic points. As can also be seen, the salts present a deep negative deviation from ideality with activity coefficients being remarkably low, while in the acid side these are close to one.

All systems studied present extreme negative deviations from the ideal solubility curve of the ammonium salt, while the experimental solubility curve of the acid is
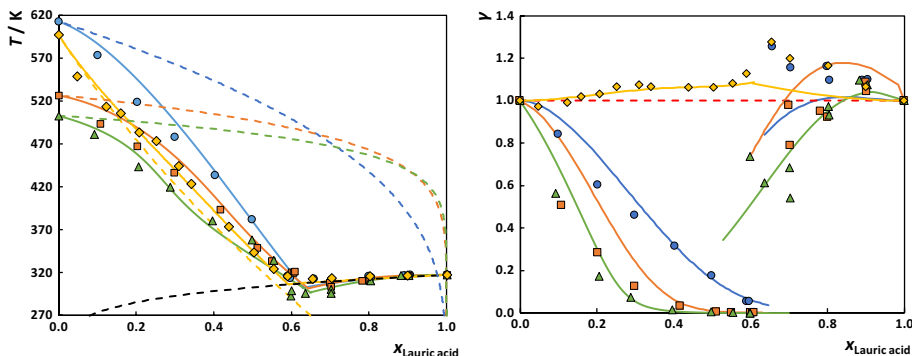
Fig. 9 Solid–liquid equilibrium and activity coefficients for lauric acid and: blue circle, $[N_{1111}]Cl$; orange square, $[N_{2222}]Cl$; green triangle, $[N_{3333}]Cl$; yellow diamond, [Ch]Cl. Solid and dashed lines correspond to PC-SAFT and ideal predictions, respectively. ($T_{m,[Ch]Cl} = 597$ K and $\Delta_m H_{[Ch]Cl} = 4.3$ kJ·mol^{-1} [44]; $T_{m,[N1111]Cl} = 612.87$ K and $\Delta_m H_{[N1111]Cl} = 20.49$ kJ·mol^{-1}; $T_{m,[N2222]Cl} = 526.78$ K and $\Delta_m H_{[N2222]Cl} = 51.24$ kJ·mol^{-1}; $T_{m,[N3333]Cl} = 503.07$ K and $\Delta_m H_{[N3333]Cl} = 66.58$ kJ·mol^{-1} [18]) (Color figure online)

almost ideal. This indicates that, in fact, these systems can be called deep eutectic solvents. When comparing these results with those obtained for [Ch]Cl + fatty acids [19], found to be quasi-ideal in both sides of the SLE phase diagram, it is possible to suggest that the extra hydroxyl group in the choline cation hinders somehow the formation of strong interactions between HBD and HBA leading to nearly ideal liquid mixtures [19].

4 Conclusions and Perspectives

So far the definition of a deep eutectic has not yet been clearly established and there are many systems reported as such that are not. This work is a contribution to establish the foundations to define, interpret and understand the DES denomination from a thermodynamic point of view. It suggests the fundamental properties needed and approaches to guarantee that a certain mixture can be really considered as a DES. As it has been shown, DES is not a new pure compound, but a mixture, that in some cases can even be modified, by adding water for instance, to improve their physicochemical properties as well as to enlarge the temperature range in the liquid state. However, it has also been pointed out that even very low water mass fraction mixtures can form mixtures with a very high water mole fraction, being so aqueous solutions.

It is suggested that to characterize a certain mixture as DES the phase diagram should be known in order to compare the real temperature depression to that observed if ideality is assumed, and to define the range of compositions for which the mixtures obeys the desired physical state and properties for a good solvent performance. Contrarily to what is found often in the literature, DES is not only formed at a given stoichiometric proportions, many times connected to very strong hydrogen bonding and complex formation, but in a mole fraction range for each mixture.

In this way, hydrogen bonding cannot guarantee the formation of a DES, nor is their presence compulsory when a DES is formed, as the ethanol + water system can illustrate. Although aqueous solutions of ethanol may have melting points as low as 155.15 K and a hydrogen bond between water and ethanol is present, the system presents positive deviations from ideality. It has also been shown, using choline chloride as the main example, that the dominant factor for the temperature depression can be the melting properties of the pure compound only.

Considering the published works up to the present date, we may say that the future of deep eutectic solvents is quite promising, and this work shows that there are other compounds that can be used to formulate these solvents besides [Ch]Cl. However, this work calls for improvements in the availability of reliable experimental physicochemical data, namely the measurement of SLE phase diagrams and their modeling—including the melting properties of the pure compounds, considering also the description of the heat capacity change with the temperature, which are extremely important and for which the scientific community should pay more attention. Is important to stress that to guarantee low melting points in the mixtures, in many cases, more critical than the interaction between the components of a mixture, are the thermophysical properties of the pure compounds. These allow the calculation of the ideal solubility lines, the development of models to describe properties and phase behavior, and give knowledge about the range of compositions and temperatures for operating these systems.

Regarding the works analyzed here, devoted to the analysis and characterization of the SLE phase diagrams of simple and deep eutectic mixtures, is possible to conclude that only

a few mixtures present negative deviations to ideality in both sides of the diagram, even if a certain degree of uncertainty persists due to the lack of reliable data concerning the properties of the corresponding pure compounds.

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