Differences on the impact of water on the deep eutectic solvents betaine/urea and choline/urea

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ABSTRACT

The differences on the impact of water on the intermolecular interactions present in the deep eutectic solvents betaine/urea and choline/urea are investigated in this work by measuring the solid–liquid phase diagrams of these mixtures with different amounts of added water. These data are analyzed in terms of ternary systems, rather than the usual pseudo-binary approach, and are used to calculate activity coefficients, which provide precious insight into how water affects the interactions of these systems. It is found that the addition of water greatly enhances the intermolecular interactions of betaine/urea near its eutectic composition, hinting at the formation of a 1:1:1 betaine/urea/water aggregate. On the other hand and contrary to what is commonly believed, water has an asymmetric impact on the interactions present in the choline/urea system. The addition of water to choline-rich mixtures leads to weaker interactions, whereas its addition to urea-rich mixtures leads to stronger interactions. This shows that the decrease in the melting temperature of choline/urea mixtures due to the presence of water does not necessarily mean that intermolecular interactions are strengthened. Finally, a minimum in the activity coefficient of urea in the choline/urea system with 2 wt. % of water was found, which coincides with several anomalies in the properties of this system previously reported in the literature.

I. INTRODUCTION

Deep eutectic solvents (DESs) are a class of green solvents introduced by Abbott et al. in 2003.¹ DESs are commonly prepared by physically mixing solid compounds, usually a hydrogen bond donor (HBD) and a hydrogen bond acceptor (HBA), resulting in a liquid at or near room temperature.²-⁴ The liquid DES arises not due to a chemical reaction but due to the formation of an eutectic-type system, where the melting temperature of the mixture is lower than the melting temperature of the pure components. Because most organic compounds form eutectic-type systems when mixed, the term DES is reserved to those mixtures that display large negative deviations from thermodynamic ideality, a trait that results in deep melting temperature depressions.⁵

A major drawback of deep eutectic solvents is their high viscosity, which hinders their application in industrial processes. To solve this problem, it is commonplace to add water to such systems in order to decrease their viscosity. For instance, a water mole fraction of 0.15 in the prototypical deep eutectic solvent reline, which is a 1:2 (molar ratio) mixture of cholinium chloride (ChCl) and urea, leads to a tenfold decrease in its viscosity.⁷ This led to many studies on the impact of water on the properties of deep eutectic solvents, and the matter has been extensively investigated in the literature, in particular, for the ChCl/urea system.⁷-¹⁷ Unfortunately, the vast majority of these studies only investigate a particular molar ratio of ChCl/urea (usually the 1:2 molar ratio), use high quantities of water, and focus their analysis on pseudo-binary systems, which hinders a fundamental understanding of the impact of water on the intermolecular interactions present in the initial systems.

Recently, while investigating the ability of betaine to act as a hydrogen bond acceptor in the formation of deep eutectic solvents, we reported that the addition of a small amount of water to the betaine/urea DES significantly decreases its melting temperature, most likely due to the formation of a strong betaine/urea/water complex or aggregate.¹⁸ No such aggregate has been reported for the ChCl/urea system, despite their similarities. Furthermore, the formation of stronger interactions in the presence of water is at odds with the view that water universally decreases the viscosity of DES, as stronger interactions between the compounds of a mixture usually...
lead to larger, rather than smaller, viscosities. These discrepancies call for a detailed study on the impact of water on these two deep eutectic solvents.

The goal of this work is to understand the impact of water on the intermolecular interactions of the systems ChCl/urea and betaine/urea in their entire composition range (see chemical structures in Fig. 1). To do so, the solid–liquid phase diagrams of the systems ChCl/urea and betaine/urea with 1, 2, 5, and 10 wt. % of water were measured and compared to the solid–liquid phase behavior of the dry systems. These weight percentages correspond roughly to water mole fractions of 0.05, 0.1, 0.3, and 0.4, respectively. Solid–liquid data are particularly useful because activity coefficients can be calculated from them, opening a window to understand the change in interactions of these systems in the presence of water and whether these interactions are strengthened or weakened, as will be analyzed in this work.

II. EXPERIMENTAL DETAILS

A. Chemicals

Trimethylglycine (betaine), cholinium chloride (ChCl), and urea were used in this work. Their CAS number, supplier, purity, and melting properties are listed in Table I. Betaine and ChCl were dried under vacuum (0.1 Pa at room temperature for at least 72 h) before use due to their hygroscopicity. Their water content after drying was measured using a Metrohm 831 Karl Fischer coulometer, with the analyte Hydranal Coulomat AG from Riedelde-Haen, and found to be around 400 ppm for betaine and 600 ppm for ChCl. Ultrapure water obtained using a Milli-Q plus 185 water purification apparatus was used to prepare the wet mixtures.

B. Solid–liquid phase diagrams

The solid–liquid phase diagrams of the systems ChCl/urea and betaine/urea with 1, 2, 5, and 10 wt. % of water were experimentally measured in this work. The appropriate amount of each DES precursor was weighed using an analytical balance (model ALS 220–4 N from Kern) with a readability of 0.1 mg, and mixtures were prepared to cover the entire concentration range of each system, from a mole fraction of 0.1–0.9 in 0.1 intervals. Then, the appropriate amount of water was added to each sample and the water content of the final mixture was checked using the same Karl Fischer coulometer methodology described in Sec. II A.

After preparation, each mixture was melted by heating under stirring to obtain a homogeneous sample and then allowed to recrystallize at room conditions. The resulting solid was pulverized with a mortar and pestle to fill glass capillaries. Due to the hygroscopicity of both betaine and choline, this procedure was done inside a dry-argon glovebox to avoid water contamination. Finally, the melting temperature of each sample was measured using a melting point device model M-565 from Büchi (temperature resolution of 0.1 K) with a temperature gradient of 0.1 K/min. The melting temperature was taken as the temperature at which complete fusion is observed and was measured three times for each mixture. The standard deviation of each data point was calculated from these measurements and found to be inferior to 1 K for all cases.

In some cases, the mixtures did not recrystallize at room temperature and their melting temperature was obtained using differential scanning calorimetry (DSC). In two instances, a melting temperature was obtained using differential scanning calorimetry (DSC). For that purpose, 5 mg of the samples were weighed using a micro-analytical balance AD6 (PerkinElmer, USA, precision of 2 μg) and tightly sealed in aluminum pans. A Hitachi DSC7000X model, working at atmospheric pressure, coupled with a cooling system, was used to perform the measurements. The cooling and heating rates were, respectively, 5 and 2 K/min, and each temperature was taken as the peak temperature upon heating. The DSC equipment had been previously calibrated with several standards (heptane, octane, decane, 4-nitrotoluene, naphthalene, benzoic acid, diphenylacetic acid, indium, tin, caffeine, lead, zinc, potassium nitrate, water, and anthracene) with purities higher than 99 wt. %. As reported in the supplementary material, some points did not crystalize even when different cooling–heating cycles were used.

C. Thermodynamic modeling

The solid–liquid equilibrium of a eutectic-type system without solid–solid transitions and whose components crystalize into their pure solid phases is described by the following equation:

$$
\Delta_{m} h(T, m) = m \Delta h_{m}(T) + (1 - m) \Delta h_{v}(T) - \Delta h_{m}(1) - \Delta h_{v}(0)
$$

![Chemical structures of the two hydrogen bond acceptors, betaine (left) and ChCl (middle), and the hydrogen bond donor, urea (right), investigated in this work.](image-url)
\[
\ln(x_i \gamma_i) = \frac{\Delta_m h_i}{R} \left( \frac{1}{T_{m,i}} - \frac{1}{T} \right) + \frac{\Delta_m C_p,i}{R} \left[ \frac{T_{m,i}}{T} - \ln \left( \frac{T_{m,i}}{T} \right) \right] - 1 ,
\]

where \(x_i\) is the mole fraction of the generic component \(i\), \(\gamma_i\) is its activity coefficient in the liquid mixture, \(\Delta_m h_i\) is its enthalpy of fusion, \(T_{m,i}\) is its melting temperature, and \(\Delta_m C_p,i\) is its heat capacity change upon melting, while \(R\) is the ideal gas constant and \(T\) is the absolute temperature of the system.

Equation (1) is often simplified by ignoring its \(\Delta_m C_p,i\) term.\(^{23,24}\) This approximation stems from its negligible contribution when compared to the \(\Delta_m h_i\) term and the scarcity of \(\Delta_m C_p,i\) values in the literature and has been validated numerous times before.\(^{5,22–24}\) Thus, Eq. (1) may be simplified to

\[
\ln(x_i \gamma_i) = \frac{\Delta_m h_i}{R} \left( \frac{1}{T_{m,i}} - \frac{1}{T} \right) .
\]

Equation (2) is used in this work to calculate the ideal solid–liquid phase diagrams of the systems betaine/urea and ChCl/urea by setting \(\gamma_i = 1\) and using the melting properties listed in Table I. Equation (2) can be rearranged to calculate activity coefficients from experimental solid–liquid equilibrium data,

\[
\gamma_i = \exp \left[ \frac{\Delta_m h_i}{R} \left( \frac{1}{T_{m,i}} - \frac{1}{T} \right) \right] .
\]

Note that in this work, Eq. (3) is applied using real mole fractions in the ternary systems (betaine or ChCl, urea, and water) rather than using water-free basis compositions.

It is worth noting that ChCl and betaine decompose upon melting, which prevents the direct experimental measurement of their enthalpies of fusion. The values listed in Table I for this property, taken from the literature,\(^{9,10,18,19}\) were indirectly estimated using solid–liquid equilibrium data and have been validated in previous works.\(^{5,15}\)

### III. RESULTS AND DISCUSSION

This section starts with the discussion of the experimental solid–liquid data obtained in this work by considering the systems as pseudo-binary mixtures, as often done in the literature. The solid–liquid phase diagrams for the systems betaine/urea and ChCl/urea, with and without added water, are depicted in Fig. 2 and the experimental data are reported in the supplementary material. The systems betaine/urea, betaine/urea + 2 wt. %, and ChCl/urea were previously reported in the literature.\(^{18,25}\)

Figure 2 reveals that water decreases the melting temperature of both systems. This has been known for a long time for the ChCl/urea system at a 1:2 molar ratio.\(^{9–17}\) However, it is interesting to note that the addition of water to ChCl/urea decreases the melting temperature in the urea-rich side but has a negligible effect on the melting temperature in the ChCl-rich side. Furthermore, the impact of water is much more notorious on betaine/urea, where as little as 2 wt. % of added water suffices in achieving a 135 °C melting temperature depression at a betaine mole fraction of 0.4. Note that it was not possible to measure the melting temperature of several mixtures with high water content and compositions close to the eutectic point due to crystallization issues, as explained in Sec. II B and listed in the supplementary material.

Figure 2 also reinforces that the solid–liquid phase diagrams of neat betaine/urea and neat ChCl/urea (no added water) are different. In neat betaine/urea, both components display strong negative deviations to ideality (experimental melting temperatures are much lower than the ideal solid–liquid phase diagram). However, in neat ChCl/urea, the experimental and ideal melting temperatures are the same for ChCl-rich mixtures, with only urea displaying negative deviations to ideality in urea-rich mixtures. This is rationalized by considering the chemical structures of both hydrogen bond acceptors (Fig. 1) and has been extensively discussed by us before.\(^{14}\) Betaine possesses a strong hydrogen bond acceptor site (the negatively charged carboxylate group) and no hydrogen bond donating site (the positively charged central nitrogen atom is highly shielded by the four methyl groups). Thus, the hydrogen bonding between betaine and urea is stronger than any interaction betaine establishes.
with itself, leading to its negative deviations to ideality. On the other hand, ChCl possesses a hydrogen bond accepting site (the chloride anion) but also a strong hydrogen bond donning site (the OH group of the cholinium cation). Thus, the interactions the chloride establishes with urea are of the same magnitude as the interactions the chloride establishes with the cholinium cation, leading to an ideal behavior for ChCl when mixed with urea. This asymmetry in behavior may provide clues on why water impacts both systems differently, as will be seen below.

The melting temperature of a eutectic-type system depends not only on its intermolecular interactions (represented by the activity coefficients of its components) but also on its composition, as Eq. (2) shows. Studying the impact of water using simple solid–liquid diagrams, such as those depicted in Fig. 2, where water-free basis mole fractions are used, does not provide insight into how the initial interactions of the DES change in the presence of water. In fact, it cannot be assumed that the impact of water on the melting temperature of these systems is due to changes in the interactions of the DES. The melting temperature decrease could be simply due to the change in composition of the system rather than the formation of meaningful interactions. In other words, water could simply decrease the mole fraction of the DES components, leading to a decrease in the melting temperature of the system, as predicted by Eq. (2). To test this hypothesis, Fig. 3 depicts the solid–liquid diagrams of the systems being studied in this work but plotted as a function of the correct mole fraction of the DES component, accounting for the presence of water.

The analysis of Fig. 3 is more complex than that of Fig. 2, especially for the betaine/urea system, but the calculation of the activity coefficients isolates the impact of intermolecular interactions from the impact of composition changes. For the ChCl/urea system, it can be observed that water has a negative impact on the interactions of the system on the ChCl-rich side. As Fig. 3(c) reveals, the addition of water actually increases the melting temperature of the ternary system, with Fig. 3(d) showing that the activity coefficients of ChCl gradually increase as the water content increases. This reveals that the presence of water leads to interactions that are less favorable to ChCl, when compared to the anhydrous deep eutectic solvent. Recall that in Fig. 2, no significant changes in the melting temperature of the ChCl-rich side were registered, meaning that the unfavorable effect of intermolecular interactions cancels out the favorable effect of composition change, leading to no melting temperature difference when the system is analyzed in terms of water-free basis compositions.

Because the systems depicted in Fig. 3 are ternary systems, it is easier to present this information in ternary diagrams. As such,
Fig. 4 depicts the ternary solid–liquid phase diagrams of the systems betaine/urea/water and ChCl/urea/water, along with the corresponding activity coefficients. Note that these are the same experimental data reported in Fig. 3, along with complementary data taken from the literature to populate the diagrams.

Figure 4 is simply another way of representing the data depicted in Fig. 3. However, these ternary diagrams reveal interesting phenomena upon careful inspection. The ternary diagram of the activity coefficients for the betaine/urea/water system reveals the presence of a strong valley around a 1:1 mole ratio of betaine and urea with a water mole fraction of 0.1. The existence of this valley was difficult to see using Fig. 3 but is clearly represented in Fig. 4. Furthermore, there seems to be an activity coefficient valley in the ChCl/urea system, for a water mole fraction of 0.1 and a urea mole fraction range from 0.7 to 0.9. The fact that these activity coefficient depressions occur at specific water compositions may indicate the formation of complexes where water plays a central role. This will be further discussed below.

The activity coefficient valleys mentioned in the previous paragraph are difficult to discuss and analyze using just Fig. 4, and it may be more useful to depict the changes in activity coefficients as a function of water mole fraction. These are depicted in Fig. 5 for the betaine/urea system.

Figure 5 is a better tool to understand the impact of water on the betaine/urea system than Fig. 3, as it isolates the contribution of water to the activity coefficients of the system. Figure 5(a) reveals that the addition of water does not significantly impact the activity coefficient of betaine for betaine-concentrated systems (water-free
basis betaine mole fractions between 0.6 and 0.9). However, there is a dramatic change at betaine mole fractions of 0.5 and 0.4. At these initial compositions, the addition of a small amount of water leads to a dramatic decrease in the activity coefficient of betaine. This corresponds to the activity coefficient valley seen in Fig. 4 for this system, and its origin is yet unclear.

The activity coefficient depression described in the previous paragraph is unlikely to be caused by the formation of new solid phases since this would be seen as a discontinuity in the liquidus lines depicted in Figs. 2 and 3, which appear fully monotonous. In addition, no abnormalities were found in the thermograms of the data points measured by DSC. Thus, such a strong activity depression hints at the formation of especially strong intermolecular interactions, and the fact that it only occurs around a 1:1 molar ratio of betaine and urea suggests the formation of a water-mediated aggregate between these two species. This aggregate could be the 1:1:1 complex identified by us in a previous work, where water functions as a bridge between urea and betaine by establishing two hydrogen bonds with both compounds, one with the oxygen of betaine and the other with a proton of urea. This aggregate is stronger than a simple betaine/urea hydrogen bond, and its existence, which is corroborated by the experimental evidence presented in this work, could help explain the role of betaine as an osmolyte and add significance to the view of betaine/urea as a natural deep eutectic solvent.

Figure 5(b) shows that water also decreases the activity coefficient of urea, although the change is not as sharp as in the case of betaine. Unfortunately, the recrystallization issues mentioned in Sec. II B prevented the calculation of more activity coefficients and not much can be inferred from the data. Nevertheless, it is clear from Fig. 5 that water strengthens the intermolecular interactions of betaine/urea regardless of its composition, in contrast to what happens in the ChCl/urea system.

Having studied the impact of water on the betaine/urea system, it is time to turn our attention to the system ChCl/urea. The activity coefficients of ChCl and urea as a function of the mole fraction of water are depicted in Fig. 6. To better understand the changes in
the activity coefficient of urea depicted in Fig. 6(b), the solid–liquid equilibrium of the system ChCl/urea with 3 wt. % of water was also measured in this work for initial ChCl mole fractions of 0.1, 0.2, and 0.3. These data are reported in Table S9 of the supplementary material.

As expected from the discussion of Figs. 3 and 4, Fig. 6(a) reveals that water has a negative impact in the intermolecular interactions of ChCl, with its activity coefficient increasing with the amount of added water, regardless of the initial composition of the system. This is in sharp contrast with the behavior seen in the betaine/urea system. However, the most significant phenomenon is depicted in Fig. 6(b). This figure reveals the existence of a minimum in the activity coefficient of urea around a water mole fraction of 0.08 (2 wt. % of water). This corresponds to the activity coefficient valley in the ChCl/urea system for a water mole fraction of 0.1 and a urea mole fraction range from 0.7 to 0.9, depicted in Fig. 4. Recall that lower values of activity coefficients for any component mean that the interactions of that component are stronger than in the original mixture. As explained above in the case of betaine, this activity coefficient minimum is also unlikely to be caused by the formation of new solid phases as they would be visible in the liquidus lines depicted in Figs. 2 and 3.

Most studies on the impact of water on ChCl/urea do not report the phenomenon depicted in Fig. 6(b) because they are not focused on such small amounts of water, nor are activity coefficients studied. However, Shah and Mjalli reported that at around 2.5 wt. % of water (corresponding to a water mole fraction of 0.1), for a ChCl/urea mixture with an initial molar ratio of 1:2, there is a maximum in the number of hydrogen bonds between urea–urea and urea–cholinium. This suggests that the presence of water somehow favors new interactions between these species. This could be due to the preferential solvation of chloride anions, which were previously interacting with urea and cholinium cations, forcing the existence of new urea–urea and urea–cholinium interactions, but it is unclear how these are stronger than urea–Cl interactions. Another explanation is the existence of a ChCl/urea/water aggregate similar to the betaine/urea/water aggregate discussed above. The existence of such an aggregate where water bridges urea–urea and urea–cholinium interactions would explain both the activity coefficient minimum and the maximum in the number of hydrogen bonds reported by Shah and Mjalli.

Other anomalies at this composition have also been reported. Al-Murshedi et al. described an inflexion point on the viscosity of reline as a function of water content around 2 wt. % of water. The same authors also report a steep increase in the surface tension of reline between 0 and 3 wt. % of water, after which it becomes approximately constant. Shah and Mjalli also observed a maximum in the relative change of the pH of reline at around 2 wt. % of water. The minimum in the urea activity coefficient may be related with, and help explain, the anomalous physicochemical properties of ChCl/urea at around 2 wt. % of water. Further studies on this subject are ongoing and will be object of a future report.

IV. CONCLUSIONS

In this work, the impact of water on the intermolecular interactions of the deep eutectic solvents betaine/urea and choline/urea was studied using solid–liquid equilibrium data. It was shown that the common way of studying these ternary systems, which is by assuming a pseudo-binary system, leads to the erroneous interpretation that a decrease in melting temperature in the presence of water must be caused by the formation of stronger intermolecular interactions. In fact, the data reported in this work show that the addition of water leads to an increase in the activity coefficient of cholinium chloride in the choline/urea system, meaning that its interactions in the deep eutectic solvent are weaker, not stronger, in the presence of water.

In contrast with the choline/urea system, the presence of water greatly decreases the activity coefficients of betaine and urea in the betaine/urea deep eutectic solvent, especially at compositions close to a 1:1 molar ratio. This corroborates the existence of a particularly strong 1:1 betaine/urea/water aggregate that could explain the physiological behavior of betaine as an osmolyte and strengthens the view of betaine/urea as a natural deep eutectic solvent.

A minimum in the activity coefficient of urea was, for the first time, identified in ChCl/urea mixtures rich in urea at very low water concentration. This coincides with anomalies in the properties of choline/urea (1:2 ratio) previously reported in the literature at this water content. The causes and the impact of this minimum in the physical properties of this deep eutectic solvent are still unknown, and further investigation is ongoing.

Finally, this work shows that focusing on specific molar ratios of deep eutectic solvents, namely, the 1:2 ratio of choline and urea, and high quantities of water hinders the full understanding of the intermolecular interactions of these systems and the impact that water has on them, even at very low concentrations.

SUPPLEMENTARY MATERIAL

The supplementary material contains all the experimental data measured in this work for each system, along with the calculated ternary mole fractions, ideal melting temperatures, and activity coefficients.

ACKNOWLEDGMENTS

This work was developed within the scope of the project CICECO-Aveiro Institute of Materials, Nos. UIDB/50011/2020 and UIDP/50011/2020, financed by national funds through the Portuguese Foundation for Science and Technology/MCTES. I.P.S. acknowledges FCT for her Ph.D. grant (No. SFRH/BD/135976/2018).

DATA AVAILABILITY

The data that support the findings of this study are available within the article and its supplementary material.

REFERENCES


