Liquid Structure of Single and Mixed Cation Alkylammonium Bromide Urea Deep Eutectic Solvents

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Abstract

The liquid structures of three alkyl ammonium bromide and urea DESs, ethylammonium bromide : urea (1:1), butylammonium bromide : urea (1:1) and ethylammonium bromide : butylammonium bromide : urea (0.5:0.5:1), have been studied using small angle neutron diffraction with H/D substituted sample contrasts. The diffraction data was fit using Empirical Potential Structure Refinement (EPSR). Amphiphilic nanostructure was found in all DESs due to cation alkyl chains being solvophobically excluded from charged domains, and clustering together. The polar domain was continuous in all three DESs, whereas the apolar domain was continuous for the butylammonium DES and in the mixed DES, but not the ethylammonium DES. This is attributed to solvophobic interactions being weaker for the short ethyl chain. Surprisingly, the urea also forms large clusters in all three DESs. In ethylammonium bromide : urea (1:1), urea - urea orientations are mainly perpendicular, but in butylammonium bromide : urea (1:1) and the mixed system in-plane and perpendicular arrangements are found. The liquid nanostructures found in this work, especially for the ethylammonium DES, is different to those found previously for correspond DESs formed using glycerol, revealing DES amphiphilic nanostructure is sensitive to the nature of the HBD.

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Introduction

Deep eutectic solvents (DESs) are mixtures of Lewis or Brønsted acids and bases that have a significant melting point decrease at the eutectic compositions compared to the pure components.¹⁻² DES properties are similar to ionic liquids (ILs) in many ways, including low vapour pressures, non-flammability and wide liquid ranges.³⁻⁵ The main advantages of DESs compared to ILs is they can be prepared from cheap, non-toxic materials, for example cholinium chloride^{1, 6-8} or other tetraalkylammonium halide salts^{7, 9-11} mixed with urea,^{6, 9} glycerol¹¹⁻¹² or a broad selection of carbohydrates⁷⁻⁸ or carboxylic acids.^{1, 10} DESs are usually prepared through simple mixing at the eutectic composition so they are much cheaper to produce than most conventional ILs.²

DESs have attracted significant research interest as replacements for conventional molecular solvents¹³⁻¹⁶ and ILs for applications ranging from electroplating¹⁷⁻¹⁸ and electropolishing of metal surfaces¹⁹ to novel high tech applications like the preparation of metal nanoparticles.²⁰ In chemical synthesis, some DESs are potent reaction media that can act as solvent and catalyst in the same system, for example bromination of 1-aminoanthra-9,10-quinones in 1:2 (molar) choline chloride:urea (commonly referred to as reline) without the need of an additional catalyst,²¹ or the application of tailored DESs in frontal polymerization reactions where the high DES viscosity and low vapour pressure are crucial advantages.²² For this polymerization reaction, utilising choline chloride:acrylic acid (1:1.6) or choline chloride:methacrylic acid (1:2) DESs enables yields of 75 – 85%, with full recovery of the non-polymerising choline chloride.

To date, the most studied DES is reline.^{2, 23-25} The origin of the marked freezing point depression in reline has been investigated by various techniques. Small-angle neutron diffraction in combination with empirical potential structure refinement (EPSR) was used by Hammond *et. al.* to probe reline nanostructure and its hydrogen bond network.²⁵ Both urea as well as the choline cation associate strongly with the chloride ion via hydrogen bonding at 2.2 Å and 2.1 Å respectively. This establishes a complex ion comprised of one choline cation, one chloride anion and two urea molecules, which leads to charge screening of the ions. The low melting points of DESs are often attributed to this kind of charge screening effect.^{2, 26} The radial distribution functions (RDFs) determined in this work were later confirmed by a first-principles molecular dynamics study.²⁴ More recent computational studies suggest the origin of the melting point depression is more complicated than simple charge screening, and rather a complicated suite of hydrogen bond interactions control the melting point and other physical properties.²⁷ This work revealed an “alphabet soup of many

different types of hydrogen bonds” in which the urea forms hydrogen bonds with the choline cation and chloride anion, as well as with other urea molecules. The levels of charge screening found between urea-surrounded cation and anion were surprisingly low, which led to the proposition of a spacer function for the urea molecule that increases the distance between ion charge centres. Similar results were obtained for the related ethaline DES (choline chloride : ethylene glycol = 1:2) using classical and *ab initio* molecular dynamics, complemented by neutron scattering measurements. A variety of hydrogen bonds between choline chloride and ethylene glycol were described which disrupt the hydrogen bond network in pure ethylene glycol. Particularly strong hydrogen bonds between chloride and ethylene glycol hydroxyl hydrogens were found to cause increased viscosity and slower transport dynamics in ethaline compared to ethylene glycol.²⁸

We previously used neutron diffraction with EPSR fitting to study the liquid nanostructure of ethyl-, propyl- and butylammonium bromide + glycerol DESs.²⁹ In all systems, a polar domain is formed due to electrostatic and hydrogen bonding interactions between anions, cation head groups and glycerol hydrogen bond donors (HBD). This excludes the alkyl chains of the cation, which associate into a separate apolar domain. The separate polar and apolar domains percolate through the DESs in a bicontinuous, sponge-like structure analogous to that found in protic, alkylammonium ILs.³⁰ We have recently found that a 0.5:0.5:1 mixture of ethylammonium bromide (EABr) : butylammonium bromide (BABr) : urea forms a DES with a melting point of 23°C.⁹ In this work we use small-angle neutron diffraction in combination with EPSR to reveal the nanostructures of the single cation DESs EABr:U and BABr:U, and contrast these with EABr:BABr:U.

Materials and Methods

Chemicals

Ethylamine (66-72% in H₂O), butylamine (99.5%), urea (98%) and deuterium oxide (99.9% in D) were purchased from Sigma Aldrich. Concentrated hydrobromic acid (48% in H₂O) was purchased from Fluka. N-butyl-d₉-amine (98% in D) was purchased from CDN isotopes. All materials were used without further purification.

Synthesis

Alkylammonium bromide:urea DESs were synthesised as previously described in the literature.⁹ Briefly, equimolar amounts of alkylamine and HBr were reacted to obtain alkylammonium bromide salts. The salts were dried under vacuum and mixed with urea to obtain EABr:U (1:1), BABr:U (1:1) and EABr:BABr:U (0.5:0.5:1) DESs. The mixtures were dried under vacuum at 70°C until a water content <0.1% wt. (Karl Fischer titration with an 870 KF Titrino plus from Metrohm) was reached. Different contrasts of varying deuterium contents were produced as described below.

h-EABr:h-U, h-BABr:h-U and h-EABr:h-BABr:h-U were synthesised from fully hydrogenous starting materials as mentioned above, without further treatment. d₃-EABr:d₄-U, d₃-BABr:d₄-U, d₃-EABr:d₃-BABr:d₄-U were produced by adding 9-10 equivalents of deuterium oxide to fully hydrogenous DESs and stirring for 1 h to guarantee full proton exchange. The samples were dried under vacuum and the procedure repeated two more times in order to obtain good deuterium yields. d₉-BABr:h-U and h-EABr:d₉-BABr:h-U were synthesised using n-butyl-d₉-amine in the general synthesis route without any further changes. d₁₂-BABr:d₄-U and d₃-EABr:d₁₂-BABr:d₄-U were synthesised using fractions of the obtained d₉-BABr:h-U and h-EABr:d₉-BABr:h-U DESs adding 9-10 equivalents of deuterium oxide and stirring for 1 h to guarantee full proton exchange and subsequent drying under vacuum. The H/D exchange was repeated two more times to obtain good deuterium yields.

Small angle neutron diffraction experiments

Small-angle neutron diffraction experiments were performed on the Small-Angle Neutron Diffractometer for Amorphous and Liquid Systems (SANDALS) at the ISIS Neutron and Muon source at the Rutherford Appleton Laboratories, UK. Samples were loaded in Ti_{0.68}Zr_{0.32} flat plate cells with 1 mm path length and an atomic density of 0.0542 atoms/Å³ and sealed airtight with the help of Teflon o-rings. Measurements were performed at 70°C for EABr:U and BABr:U, and at 50°C for EABr:BABr:U. Data was collected for 6-8 h per contrast in order to accumulate statistically meaningful diffraction signals over a Q-range of 0.05 – 50 Å⁻¹ using neutron wavelengths from 0.05 – 4.95 Å. This

allows for analysis of atom pair distributions up to a maximum length scale of ~ 30 Å at a resolution of 0.1 Å. For calibration and normalization of the diffraction data, empty beam, empty cells and a vanadium niobium standard were separately measured.

Data correction and background subtraction³¹ were performed using the GUDRUN 2017 software package provided at <https://www.isis.stfc.ac.uk/Pages/Gudrun.aspx>.

Empirical potential structure refinement

EPSR was used to fit 3D simulation boxes onto the measured diffraction data set. The underlying theory is described in detail in reference.³² Briefly, as a first step a reference potential is derived via Monte Carlo modelling of a simulation box which is set up using physical constraints for each system such as sample composition, atom number density, intra molecular bond distances, atom charges, Lennard-Jones potentials, rotational axis and dihedral angles where appropriate. An overview of the parameters chosen in the discussed systems is shown in Table 1. The allowed particle moves in EPSR are whole molecule

Figure 1 Molecules and ions with atom labels as used for EPSR modelling.

translations, whole molecule rotations, rotation of specific molecular sidechains and individual intramolecular atomic moves. After the simulation is equilibrated, the experimental data is introduced to derive an empirical potential for a further refinement. This is done via a second Monte Carlo loop in which the structure factors ($F(Q)$) of the simulation and the diffraction experiments are compared. EPSR then rearranges the simulation box in order to converge the simulated towards the experimental structure factors. The confidence in the simulation is increased by modelling the simulation box simultaneously onto multiple experimental datasets derived from the different H/D contrasts. After a satisfactory degree of refinement is reached, the converged simulation boxes are accumulated to improve statistics (>3000 iterations). RDFs, spatial distribution functions (SDFs) and intermolecular coordination numbers and other parameters are then calculated from the accumulated simulation boxes as shown in the results and discussion section.

Table 1: Atom labels, Lennard-Jones parameters, bond distances and charges used for EPSR modelling.

Label	ϵ /kJ mole ⁻¹	σ /Å	q /e ⁻
ethylammonium			
CY	0.2763	3.50	0.190
CZ	0.2763	3.50	-0.180
HE	0.1255	2.50	0.060
NX	0.7118	3.25	-0.300
HX	0.0000	0.00	0.330
butylammonium			
CA	0.2763	3.50	0.190
CB	0.2763	3.50	-0.120
CC	0.2763	3.50	-0.120
CD	0.2763	3.50	-0.180
NN	0.7118	3.25	-0.300
HB	0.1255	2.50	0.060
HN	0.0000	0.00	0.330
urea			
CU	0.4390	3.75	0.142
OU	0.8780	2.96	-0.390
NU	0.7110	3.25	-0.542
H1	0.0000	0.00	0.333
H2	0.0000	0.00	0.333
bromide			
Br	0.8600	3.970	-1.000

Results and Discussion

Data fitting and Cluster analysis

Figure 2: Small-angle neutron diffraction data (black) and corresponding EPSR fits (colour) for EABr:U (top), BABr:U (centre) and EABr:BABr:U (bottom).

In the first part of this section we primarily focus on the features of EABr:U (1:1) and BABr:U (1:1). Once the description of these two single cation DESs is complete, we turn our attention to the nanostructure of the mixed cation system EABr:BABr:U (0.5:0.5:1).

Figure 2 shows neutron diffraction data for EABr:U and BABr:U. Multiple contrasts were prepared for each DES system which differ in their degree of deuteration but are otherwise chemically identical. The fits are in good agreement with the experimental data for $Q > 2 \text{\AA}^{-1}$. Low Q deviations in hydrogen rich contrasts are caused by inelastic scattering which leads to difficulties in the data reduction. This is a common problem in small-angle neutron diffraction experiments and the subject of ongoing research.³¹ The average R-factor, which is a measure for the quality of the fit, was ~ 0.0007 in all systems which demonstrates the model is of high quality.^{25, 29, 33-37}

The contrasts in which only exchangeable protons are deuterated (purple data sets) show sharp first diffraction peaks for both DESs. Similar “pre-peaks” have been widely reported for ILs which are amphiphilically nanostructured.³⁸ The pre-peaks for EABr:U ($0.7 \text{\AA}^{-1}$), and BABr:U ($0.45 \text{\AA}^{-1}$) correspond to real space distances of 9.0 $\text{\AA}$ and 14.0 $\text{\AA}$ respectively. This is larger than the size of

the individual ions or H-bond donor molecule and indicates the presence of long range structure in the DESs. The increase in repeat spacing of 5 Å is the same as the length of 4 methylene groups ($4 \times 1.265 \text{ Å} = 5.06 \text{ Å}$),³⁹ which is consistent with association of alkyl chains into a bilayer-like arrangement within apolar domains, and is similar to the effect previously seen in alkylammonium bromide : glycerol (1:2) DESs.²⁹

In both DESs, all contrasts exhibit a peak between $1.5 - 1.7 \text{ Å}^{-1}$, which corresponds to real space distances between 3.6 and 4.1 Å. This “contact peak” is caused by a multitude of first coordination shell interactions, such as anion–urea, anion–cation, cation–urea and urea–urea^{29, 37-38} which are described below.

Figure 3 shows snapshots of the DES simulation boxes. The first row (A-C) shows all atoms in standard colours, except for bromide which is in green for clarity; In the second row (D-F) polar groups (urea, cation ammonium and bromide) are red and the apolar cation alkyl chains are grey. The final row shows only urea molecules. These images show that bromide is evenly distributed throughout the DESs, but that urea is not. Rather, urea forms a continuous network. Figure 3D and E reveal a sponge-like network of polar and apolar domains is present in both EABr:U and BABr:U. The polar domain forms due to electrostatic attraction between cations and bromide anions as well as hydrogen bonding between urea, cation ammonium and bromide. Like in ILs^{30, 40} and some other DESs²⁹, cation alkyl chains are solvophobically excluded and associate into nonpolar regions resulting in bicontinuous amphiphilic nanostructures. Consistent with the longer cation chain length, the apolar network is larger and more pronounced for BABr:U than EABr:U.

Figure 4 presents the distribution of cluster sizes formed by various interactions between polar groups.⁴¹ Two atoms are defined as in a cluster if they are located within the first coordination shell, i.e. closer than the minimum after the first peak in the radial distribution function (RDF) (SI Table S1). Clusters associated with electrostatic interactions between bromide and ammonium nitrogen on ethylammonium (Br – NX) and butylammonium (Br – NN) cation are shown in blue, while cluster data involving hydrogen bonding is black for urea – urea (OU – NU), red for cation ammonium – urea (NX – OU/ NN – OU) and green for bromide – urea (Br – NU). The straight line in Figure 4 represents the percolation threshold for clusters of a given size.⁴²

Figure 3: Snapshots of refined simulation boxes. **A – C** Full simulation boxes (hydrogen white, carbon grey, bromide green, nitrogen blue). **D – F** Polar vs. apolar domains (cation alkyl chains grey, all other atoms red). **G – I** Urea molecules only (hydrogen white, carbon grey, oxygen red, nitrogen blue). Simulation boxes contain 1200 molecules/ ions. EABr:U = 400 ethylammonium cations, 400 bromide anions, 400 urea molecules. BABr:U = 400 butylammonium cations, 400 bromide anions, 400 urea molecules. EABr:BABr:U = 200 ethylammonium and 200 butylammonium cations, 400 bromide anions, 400 urea molecules.

The cation-anion clusters formed in both EABr:U (Figure 4A) and BABr:U (Figure 4B) overwhelmingly contain virtually all (700 – 800) ions present in the simulation, confirming the presence of a single, continuous charged or polar domain. H-bonded Br – NU clusters likewise predominantly form a continuous network containing almost all bromide and urea, whereas cation ammonium – urea preferentially form smaller clusters in both DESs. Urea-urea clusters are also consistent with an extended network, which in EABr:U clearly spans the simulation.

190 A continuous apolar domain for BABr:U is similarly revealed by butylammonium methyl group cluster analysis (Figure

Figure 4: Clusters formed by polar groups in (A) EABr:U and (B) BABr:U. Bromide – cation clusters (blue), bromide – urea clusters (green), cation – urea cluster (red), and urea – urea clusters (black). Cluster formed by terminal methyl groups in EABr:U and BABr:U (C) for ethylammonium methyl groups (blue) and butylammonium methyl groups (red). The black line in all graphs shows the percolation threshold and follows the power law $p(n) = n^{-2.2}$.

4C), which mostly contain between 300 and all 400 cations present. However, for EABr:U, while a large proportion of clusters with size $n \sim 10 - 300$ appear above the percolation threshold, the ethylammonium alkyl chains never all form a single domain. This is due to stronger solvophobic segregation of the C_4 alkyl chain.

In earlier work we found that a continuous apolar domain was present even in 1:2 EABr:glycerol DESs.²⁹ This means that the differences seen here cannot be explained by the lower apolar volume fraction in EABr:U. This confirms that the existence of a continuous apolar domain and DES amphiphilic nanostructure are sensitive to the nature of the HBD.²⁹

The less extensive networks of urea in BABr:U and methyl groups in EABr:U highlight the role of solvophobicity in determining liquid nanostructure. Stronger segregation of butyl chains arises at some cost to the integrity and extent of the urea H-bond network, which remains intact in the presence of ethylammonium. This is reminiscent of the different hydrogen bonding motifs seen in ethylammonium and butylammonium thiocyanate ILs, suggesting different local arrangements within the polar domains of EABr:U and BABr:U.⁴³

The polar domain

The polar domain networks of EABr:U and BABr:U are largely unaffected by whether the cation alkyl chain length is C₂ or C₄, (or a 50:50 mol% mixture of C₂ and C₄, see below).

Figure 5 shows the radial distribution functions (RDFs) and spatial distribution functions (SDFs) of bromide and the urea oxygen around the ethylammonium and butylammonium charge centres. In these and all following RDF plots the EABr:U system is represented as coloured dashed lines, while BABr:U and EABr:BABr:U are shown as coloured solid and grey solid lines respectively. It is important to note that all SDFs throughout this paper were calculated for rotamer averaged central molecules. This means that the SDFs do not directly provide information of correlations between the surrounding species and atoms on the central species other than the defined centre of the calculation. For clarity however, the central molecule is not shown in a rotamer averaged representation but in a standard structure representation for one possible conformation. In both systems the nearest neighbour bromide peak lies at 2.0 Å, consistent with electrostatic attractions, re-enforced hydrogen bonds. The second peak in these RDFs resolves the locations of bromide coordinating with the remaining two ammonium hydrogens.

The first peak distance in the RDFs for the urea oxygen and cation ammonium hydrogens for EABr:U and BABr:U is even shorter, at 1.7 – 1.8 Å. As urea is not charged, this is solely due to strong hydrogen bonding⁴³ between the urea oxygen and the ammonium hydrogens.

Previously we investigated the influence of cation chain length and anion type on hydrogen bonding in alkylammonium ionic liquids.⁴³ We found that the length of cation – anion hydrogen bonds was hardly affected by cation alkyl chain length (e.g. hydrogen bonds in ethylammonium nitrate and propylammonium nitrate are 2.37 Å and 2.34 Å, respectively). The fact that the length of the hydrogen bond between bromide and the ammonium hydrogens EABr:U and BABr:U is 2.0 Å in both systems is consistent with this finding.

Figure 5A and B SDFs (50% probability surfaces) show distinct overlapping lobes due to bromide (red) and urea oxygen (blue) coordinating opposite each ammonium hydrogen, with the urea oxygens associating at closer distance on average. This arrangement of anions and the HBD has been seen in related DESs^{29-30, 43}, and shows the competition of bromide and urea for ammonium head group binding sites. Probability surfaces for urea in BABr:U are smaller than in

EABr:U, revealing more defined arrangements in the polar domain in the longer cation system. This is also seen in Figure 5D, which shows the hydrogen bond angle distributions. In both EABr:U and BABr:U 65% of the bromide – cation hydrogen bonds are linear (i.e. bond angle is 165-180°.⁴³). As shorter hydrogen bonds are stronger, they tend to be straighter,⁴³ so it is surprising that the bond angle distributions for urea is broader than bromide – only 49% and 53% linear for EABr:U and BABr:U, respectively. As we shall see, this is probably a consequence of the urea amine groups also forming hydrogen bonds with nearby atoms, which pulls the urea oxygen away from the energetic minimum straight orientation;⁴³ Bromide and urea both overwhelmingly form simple, single H-bonds with the cation, with only a small fraction of bifurcated bonds (0.2-0.4%).

Figure 5C reports coordination numbers around each ammonium hydrogen. In both EABr:U and BABr:U, each ammonium hydrogen is coordinated by 0.8 bromide, yielding an overall coordination number for the ammonium group of 2.4. The corresponding coordination number of urea oxygen is 0.2 per hydrogen or 0.6 per ammonium group. Together these sum to match the results found in ethylammonium nitrate, a closely related protic ionic liquid, in which three anions coordinate with every cation. This is due to the competition between bromide and urea for binding sites with the cationic ammonium group.⁴⁴ The high bromide-cation coordination number is consistent with strong electrostatics, and the relatively small cation-urea clusters found within the otherwise well-defined polar domain (Figure 4). This is supported by the finding that correlations between bromide with cation alkyl chain carbons become weaker as the distance from the positive charge centre increases (SI Figure S2). This is most notably for bromide with the terminal carbon of the butylammonium cation (CD) which has no peak.

Figure 5: **A** Radial (left) and spatial distribution functions (right) of urea oxygen (blue) and bromide ion (red) around ethylammonium charge centre in EABr:U. **B** Radial (left) and spatial distribution functions (right) of urea oxygen (blue) and bromide ion (red) around butylammonium charge centre in BABr:U. In all radial distribution functions EABr:U is plotted as dashed coloured lines, BABr:U as solid coloured lines and EABr:BABr:U as solid grey lines. RDFs are offset for clarity. SDFs plotted as 50% probability surfaces; alkyl chains on central cations are shown as one possible rotamer conformation for clarity. **C** Coordination numbers of bromide and urea oxygen with ethylammonium headgroup hydrogens and butylammonium headgroup hydrogens as central species. **D** Hydrogen bond angle distribution of bromide (red) and urea oxygen (blue) with alkylammonium hydrogens for EABr:U (coloured dashes), BABr:U (coloured solid) and EABr:BABr:U (grey solid).

Figure 6 shows the organisation of urea within the polar network of these DESs. The RDFs for the urea oxygen around urea H1 and H2 have clear peaks at 1.9 Å (Figure 6B), indicating strong hydrogen bonding. Corresponding RDFs for bromide around H1 and H2 also both have sharp peaks but, as seen around the ammonium cation, bromide preferentially lies at a slightly greater distance, 2.2 Å in this case. This distance also closely matches results found previously for chloride with urea hydrogens in reline,²⁵ and indicates weak hydrogen bonds.

Figure 6C and D shows that 50% probability surface SDFs for the arrangements of urea oxygen (blue), bromide (red) as well as the cation ammonium charge centres (green) around a central urea carbon are all virtually identical for EABr:U and BABr:U. The bromide distribution is well defined in both, with two spherical distributions near each H1 hydrogen, and a longer lobe at the H2 side of urea. Each bromide lobe is centred at a slightly greater distance than the corresponding lobe of an overlapping H-bonded urea oxygen, confirming that, here too, they compete directly for the same H-bonding sites.

The RDF of bromide around the central carbon of urea for both EABr:U and BABr:U has a first peak at ~4.1 Å and a broader second peak at ~8 Å, which represents a second coordination shell. This indicates long range ordering between the HBD and the bromide anions. As the first solvation shell Br-CU coordination numbers are 3.2 for EABr:U and 3.6 for BABr:U, on average all three coordination sites are occupied. The corresponding urea – urea (CU-CU) coordination numbers are 4.5 for EABr:U and 4.1 for BABr:U. These values are much higher than the urea - cation (1.0 – 1.1) coordination numbers, consistent with the large urea – urea clusters shown in Figure 4, and showing that urea – urea interactions are not confined to the H-bond sites identified above.

Figure 6: **A** Radial distribution functions of bromide vs urea hydrogens and urea carbon. **B** Radial distribution functions of urea oxygen OU vs urea hydrogens and urea carbon. In all radial distribution functions EA:Br:U is plotted as dashed coloured lines, BA:Br:U as solid coloured lines and EABr:BA:Br:U as solid grey lines. Datasets are offset for clarity. **C** and **D** spatial distribution functions of urea oxygen (blue), bromide (red) and cation charge centre (green) vs urea carbon CU in EA:Br:U and BA:Br:U respectively. SDFs plotted as 50% probability surfaces. **E** Coordination numbers of bromide and urea carbon CU with different urea sites.

Figure 6C and D shows that the alkylammonium cations form a similar toroidal primary coordination shell around the urea oxygen in both DESs, consistent with the peak positions in Figure 5A and B. The second peak at larger distances occurs next-nearest neighbour ordering adjacent to the H2 (opposite) and H1 hydrogens of urea. This results from the attractions between the ammonium and bromide ions associated with urea in a urea – bromide – cation arrangement. This shows how the urea HBD is incorporated within the ion network, acting as a spacer molecule between ions (mostly between cation-bromide ion pairs) in DESs, which was hypothesised in recent studies.²⁷

Figure 7 shows urea – urea (CU – CU) correlations as a function of separation and relative orientation. Here urea is approximated as a planar molecule following previous studies.²⁵ The coordinate system for urea is defined as shown in Figure 7D. The-z axis lies orthogonal to the plane of the molecule, and θ is the angle between two z-axes.

There are striking differences between the orientation distributions in the two DESs. In EABr:U (Figure 7A) the nearest neighbour peak is clearly centred at 90° , which means the preferred orientation of urea molecules in the first coordination shell is perpendicular. Figure 7B shows that BABr:U also has a peak at 90° , but also at $0/180^\circ$. This means that in BABr:U both perpendicular and in-plane urea arrangements arise. In the crystal phase of urea,⁴⁵ as well as in aqueous urea solutions,⁴⁶ both conformations can be found. In aqueous solution the in-plane conformation is the enthalpic form which is a front-to-back arrangement of two urea molecules (Figure 7D), which enables the formation of two strong hydrogen bonds between the urea oxygen and the H1 hydrogen of both molecules. Two perpendicular urea orientations exist (Figure 7E and F), one in which the planar side of a urea molecule coordinates via weak hydrogen bonds between the H2 hydrogens and the urea nitrogens and oxygen. This orthogonal orientation has a higher degree of rotational freedom than the enthalpic form and is therefore entropically favoured. The second perpendicular orientation forms one strong hydrogen bond but has increased rotational freedom compared to the in-plane arrangement, thus is an intermediate orientation.⁴⁶ Therefore, the EABr:U system strongly favours urea molecules in their more entropic conformations, whereas BABr:U also has a large fraction of the enthalpic conformation. We propose that better defined nanostructure in BABr:U compared to EABr:U reduces the orientational freedom of urea, which disfavours the entropic conformation.

Figure 7: Angular radial distribution functions for urea-urea correlations with CU as centre. **A** EABr:U, **B** BABr:U, **C** EABr:BABr:U. Coordinate system defined with x-axis running through two nitrogen atoms with origin in the centre of the two atoms and y-axis pointing towards oxygen. The z-axis lies orthogonal to the x/y plane. The angle ϑ is defined as the angle between two z-axis. **D-F** possible urea-urea orientations, reproduced from reference.⁴⁶

The apolar domain

Figure 8 shows the arrangements of cation terminal methyl groups in EABr:U and BABr:U. The RDF in BABr:U has a broad nearest-neighbour peak at 4.0 Å with a coordination number of 5.2, and in EABr:U the primary peak lies at 3.7 Å and the coordination number is 2.5. This is consistent with stronger solvophobic segregation in the butylammonium system due to the longer cation alkyl chain, and is supported by the finding that correlation peaks between the butylammonium terminal methyl carbon and subsequent carbons along the chain become less defined the closer the

carbon atom is to the charge group (SI Figure S5). This indicates a bilayer arrangement is preferred and “head-to-tail” arrangements are improbable, consistent with results for alkylammonium bromide glycerol DESs.²⁹

These nearest-neighbour distances for terminal methyl groups are similar to those previously reported for amphiphilic ILs like ethylammonium nitrate (3.8 Å)³⁷ and propylammonium nitrate (3.7 Å),⁴⁷ and DESs like alkylammonium bromide:glycerol (3.8 Å).²⁹ EABr:U and BABr:U show broader RDF peaks for terminal methyl groups than EABr:glycerol (1:2) and BABr: glycerol (1:2), suggesting less ordered apolar domains.

Figure 8B shows 30% probability surface SDFs for cation terminal methyl groups in EABr:U and BABr:U. Methyl-methyl correlations in ethylammonium (Figure 8B, top) exhibit three small lobes similar to structures that are widely seen across amphiphilic ethylammonium ILs³⁰ and their solutions,⁴⁸ as well as in EABr:glycerol.²⁹ This is primarily a consequence of the small apolar volume in EABr:U requiring well defined locations. The corresponding structure in BABr:U (Figure 8B bottom) is larger and more evenly distributed. This is unlike the BABr:glycerol (1:2) DESs or the ionic liquid butylammonium thiocyanate³⁰, in which the methyl – methyl SDF lobes are better defined than for ethylammonium. Each terminal methyl group in BABr:U is surrounded by ~5 other methyl groups compared to 2.5 in EABr:U, 2.1 in BABr:glycerol, or 2.4 in butylammonium thiocyanate. Closer inspection reveals that the broad nearest-neighbour peak of the RDF conceals two components: three lobes close to the methyl hydrogens merge into the larger, more uniform distribution. As we discuss below, this is a novel consequence of interactions between urea and the non-polar groups.

Figure 8: A Radial distribution functions of terminal methyl groups vs terminal methyl groups for CZ-CZ (red), CD-CD (blue) and CZ-CD (green). **B** Spatial distribution functions of terminal methyl groups vs terminal methyl groups for CZ (red) vs CZ and CD (blue) vs CD in EABr:U (top) and BABr:U (bottom). The solid blue probability surface for BABr:U was calculated with a 4.5 Å cut-off distance. **C** Coordination numbers CZ and CD with CZ and CD as central species. In all radial distribution functions EABr:U is plotted as dashed coloured lines, BABr:U as solid coloured lines and EABr:BABr:U as solid grey lines. SDFs plotted as 30% probability surfaces; for clarity central molecules are represented as one possible rotamer conformation in respect to the centre of interest..

The RDFs for both ethylammonium carbons and the urea carbon have sharp peaks at 4.1 Å, and coordination numbers of 4.8 and 4.9 for the methylene and methyl carbons, respectively. The corresponding SDF shows that urea carbons are arranged around the methyl in a ring lying towards the polar ammonium group, plus some small lobes below the chain end. Urea is preferentially oriented around the cation parallel to the ring so that the methyl carbon is on the planar side close to the urea carbon, where it is charge neutral.⁴⁹

The RDFs for urea around the butylammonium methyl group (CD – CU) and α -methylene are similar, but the correlation peaks are much broader for γ and β carbons. In BABr:U, the SDF shows that the urea carbons are preferentially located below the terminal methyl (CD) and around it in three lobes. Here again the methyl group are

preferentially arranged on the planar sides of urea, although some small lobes are also present near H1 in the urea molecular plane. The lobe arrangement of CU around the terminal methyl in BABr:U actually corresponds to the relative arrangement of terminal methyl groups seen in butylammonium thiocyanate IL and in BABr:glycerol. In BABr:U, these results show there is significant contact between the cation alkyl chain and urea, which leads to competition between CU and CD, and to the less ordered overall arrangement of methyl groups. This effect is a consequence of solvophobic interactions between cation hydrocarbon groups and the urea, which can swell the larger non-polar regions of BABr:U, and explains why apolar domains are less well defined in EABr:U and BABr:U than alkylammonium:glycerol DESs.²⁹

Figure 9: **A** Radial distribution functions of ethylammonium alkyl chain vs urea carbon (CU). In all radial distribution functions EABr:U is plotted as dashed coloured lines, BABr:U as solid coloured lines and EABr:BABr:U as solid grey lines. **B** Spatial distribution functions of terminal methyl group (CZ) vs urea carbon and vice versa. All SDFs plotted as 33% probability surfaces; for clarity central molecules are represented as one possible rotamer conformation in respect to the centre of interest. **C** Radial distribution functions of butylammonium alkyl chain vs urea carbon (CU). **D** Spatial distribution functions of terminal methyl group (CD) vs urea carbon and vice versa. **E** Coordination numbers CZ and CD with urea carbon.

Mixtures of Cations

As we have previously shown, mixing cations with different alkyl chains is an effective strategy for reducing the eutectic temperature and stabilising the liquid.⁹ Here we examine how mixing equimolar EABr and BABr affects liquid nanostructure. As with the single cation DESs described above, good agreement between experimental scattering data and the EPSR modeling was obtained across four isotopic substitutions in the mixed system (Figure 2).

Scattering from d_3 -EABr: d_3 -BA:Br: d_4 -U, which shows the greatest neutron contrast between polar and apolar groups, exhibits a distinct nanostructure pre-peak at $0.49 \text{ \AA}^{-1}$, which corresponds to a real space distance of $12.8 \text{ \AA}$. Although the density of the mixed system is almost exactly the average of the two pure systems (EABr:U = 1.41 g/ml ; BABr:U = 1.30 g/ml ; EABr:BABr:U = 1.35 g/ml), this spacing is much closer to that seen in BABr:U ($14.0 \text{ \AA}$) than EABr:U ($9.0 \text{ \AA}$). The nearest neighbour or contact peaks^{29, 37-38} appear between $1.6 - 1.7 \text{ \AA}$ which are in the same range as for EABr:U and BABr:U, suggesting that the polar domain is not significantly affected by mixing cations. This is consistent with Figure 5 and Figure 6, in which RDFs, and coordination numbers for EABr:BABr:U are shown to be almost identical to the single cation DESs. Mixing cations of different alkyl chain lengths has negligible impact on correlation distances in the polar domain. This is also seen by comparing SDFs for EABr:BABr:U (SI Figure S3 and S4) with those of EABr:U and BABr:U (Figure 5A and B, Figure 6C and D).

The polar domain cluster distributions in EABr:BABr:U (Figure 10A) are also more like that of BABr:U than EABr:U (Figure 4). Clusters comprising bromide and both cation charge centres are almost exclusively a single, box-spanning network, as they are in both pure cations DESs. While bromide-urea also form large clusters in the mixed DES, like BABr:U they are smaller than the simulation box, and none incorporate all molecules. Similarly, urea-urea clusters in EABr:BABr:U adopt a broad distribution ranging from ~ 5 - 350 , which is more like BABr:U than EABr:U. Urea forms only small clusters with the ethylammonium and butylammonium nitrogen cations, similar to those seen in EABr:U and BABr:U (Figure 4A and B), with no apparent preference.

Although some differences are seen between RDFs within the polar domains of these DESs, the similarity of the mixture to BABr:U is clearest in the urea-urea angular RDFs (Figure 7). Like BABr:U, EABr:BABr:U (Figure 7C) shows a clear entropic or perpendicular peak orientation at 90° as well as an enthalpic or in-plane peak at $0^\circ/180^\circ$ that is not seen in EABr:U. This shows that at equal amounts of ethylammonium and butylammonium, the butylammonium alkyl chain has sufficient impact on the rotational freedom of urea to favour energetic in-plane orientations between urea

molecules. This is consistent with the strong resemblance of EABr:BABr:U and BABr:U the cluster analyses (Figure 4A and B and Figure 10A).

A Polar clusters EA:BA:Br:U

C vs CZ vs CD

D VS VS

E VS VS

B Non-polar clusters

Figure 10: **A** Cluster analysis for polar interactions. Bromide – cation clusters (blue), bromide – urea clusters (green), cation – urea cluster (red), and urea – urea clusters (black). **B** Cluster formed by terminal ethylammonium methyl groups (red), butylammonium methyl groups (blue), mixed clusters between ethyl and butyl (green) and combined clusters (black). The black line in the cluster plots shows the percolation threshold and follows the power law $p(n) = n^{-2.2}$. **C** SDFs for ethylammonium terminal methyl group (red) and butylammonium terminal methyl group (blue) vs terminal methyl groups CZ and CD, plotted as 30% probability surfaces. **D** SDFs for ethylammonium terminal methyl group vs urea and vice versa, plotted as 33% probability surfaces. **E** SDFs for butylammonium terminal methyl group vs urea and vice versa, plotted as 33% probability surfaces. For clarity central molecules are represented as one possible rotamer conformation around the centre of interest.

Figure 10B shows that terminal carbons from ethyl and butyl chains primarily associate together into a single, large, mixed-chain apolar domain, with only little contribution from small to medium sized clusters. This is most like the single apolar domain that dominates BAb:U, rather than the broad distribution of finite clusters seen in EAb:U (Figure 4). Within this apolar domain, only finite clusters of ethyl-ethyl, butyl-butyl, or ethyl-butyl mixtures are seen. Butylammonium terminal groups (blue) form bigger clusters than the ethylammonium groups (red), which reflects a bilayer-like local organisation; methyls on longer butyl chains have more opportunity for solvophobic association with other terminal methyls. Surprisingly, ethyl – butyl terminal carbon clusters are larger than ethyl – ethyl or butyl – butyl, suggesting a high degree of mixing and little segregation of unlike cations.

The terminal methyl group RDFs (Figure 8A) show some of the clearest differences between EAb:BAb:U and the single cation DESs. The butylammonium methyl nearest-neighbour peak lies at the same distance in the mixture as in BAb:U, but the signal is much sharper. The corresponding RDF of ethylammonium methyl groups exhibits a peak at 4.0 Å, which is 0.3 Å larger than in EAb:U, and the ethylammonium-butylammonium terminal methyl RDF also has a peak at 4.0 Å. The packing of cation chain ends within the apolar domain is completely shifted towards BAb:U even in a 1:1 mixture.

SDFs for the mixed system (Figure 10C) show that ethylammonium methyl groups are less ordered in the mixed system around both ethyl and butyl chain ends. In contrast, butylammonium methyl groups are exclusively arranged in a small area opposite the very end of ethylammonium alkyl chains. This means that butylammonium alkyl chains do not intercalate with ethylammonium alkyl chains, which is probably due to solvophobic repulsion caused by the proximity of the ammonium charged group and its polar domain. The butylammonium methyl groups are evenly distributed about each other (Figure 10C), which is identical to their distribution in BAb:U (Figure 8B). Ethylammonium methyl groups form lobes around the butylammonium methyl carbon that almost fuse into a ring. This suggests that the apolar domain in EAb:BAb:U is formed by solvophobic exclusion of butyl chains among which ethyl chains are dissolved.

Figure 9A and C show RDFs between the urea carbon and ethylammonium or butylammonium terminal methyl groups, respectively. Figure 9A shows the ethylammonium terminal methyl group – urea peak position is the same in the

mixture as in EABr:U, and Figure 9B shows the butylammonium peak positions is only 0.1 Å larger in EABr:BABr:U. Thus, cation terminal methyl group correlation distances are almost identical in all three DESs.

Figure 10D shows the different distributions of urea around the two cation chains in the mixed system. Urea is distributed around the ethylammonium methyl group in an equatorial ring, as it is in EABr:U, but with a slightly more pronounced lobe below the carbon atom. Around the butylammonium methyl group (Figure 10E) urea preferentially occupies three lobes below the methyl group that fuse into an equatorial ring distribution that is less well defined than in pure BABr:U (Figure 9D). As in EABr:U and BABr:U, the SDFs of the two terminal methyl groups around the urea carbon in EABr:BABr:U Figure 10D and E are limited to the planar sides of the urea molecule. This shows that the uptake of urea molecules into the apolar domains of BABr:U also occurs in EABr:BABr:U.

The reason that the urea-urea orientations are affected by the cation chain lengths (or mixing of cations) while the rest of the polar domain structure is seemingly the same in the three DESs is due to the cation alkyl chains associating closely with the planar sides of the urea molecule. The polar binding sites (NH₂ groups and oxygen) remain largely unoccupied by alkyl chains.

Conclusion

Despite significant research into DESs as alternatives to conventional solvents, the origin of their outstanding liquid properties is still under debate. Little research exists that directly probes liquid nanostructure of DESs^{25, 29}, with no work to the author's knowledge addressing the effect of mixing cations. Here we have shown that EABr:U, BABr:U, and EABr:BABr:U are amphiphilically structured, with bicontinuous polar and non-polar domains, due to solvophobic segregation of cation alkyl chains. The polar domains are characterised by a variety of hydrogen bond and electrostatic interactions (i.e., cation – bromide, cation – urea, bromide – urea and urea – urea). In the apolar domain, solvobic segregation is stronger for butylammonium than ethylammonium, which leads to larger domain sizes and alkyl chain clusters. The radial and spatial distribution functions as well as cluster analysis showed that the apolar domain of the mixed cation DES more closely resembles that of BABr:U than EABr:U.

The polar domain structure is essentially identical in EABr:U, BABr:U, and EABr:BABr:U. Bromide and urea (via its oxygen atom) compete for the same binding sites on the cation charge centre as well as other urea molecules with urea consistently showing shorter bond distances. This substantiates the importance of HBD interactions within DESs. SDFs showed complex arrangements between cations, anions and urea molecules that place urea between charged groups. This suggests urea has a spacer function between ions and supports the hypothesis of previous studies.²⁷ The orientation between urea molecules shifted from a mainly (entropic) perpendicular orientation in EABr:U to a mixture of perpendicular and in-plane (enthalpic) arrangements in BABr:U and EABr:BABr:U.

The EABr:U and BABr:U liquid nanostructures differ in several respect from the same salts with a glycerol HBD. A key reason for this is the surprising tendency for cation methyl groups and the urea carbon to associate. This shows that not only is DES nanostructure dependent on the HBD type, but that the interactions that drive the differences can be difficult to predict.

Supporting Information

The Supporting Information is available free of charge online.

Peak position ($r_{\max}$), peak minimum used for calculation of coordination numbers ($r_{\min}$), coordination number and standard deviation; Radial distribution functions and spatial density functions.

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