Theoretical study of Ionic Liquids based on the Cholinium cation. Ab-initio simulations of their condensed phases.

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ABSTRACT

We have explored by means of *ab-initio* molecular dynamics the homologue series of 11 different Ionic Liquids based on the combination of the cholinium cation with deprotonated amino acids anions. We present a structural analysis of the liquid states of these compounds as revealed by accurate *ab-initio* computations of the forces. We highlight the persistent structural motifs that see the ionic couple as the basic building block of the liquid whereby a strong hydrogen bonding network substantially determines the short range structural behavior of the bulk state. Other minor docking features of the interaction network are also discovered and described. Special cases along the series such as Cysteine and Phenylalanine are discussed in the view of their peculiar properties due to zwitterion formation and additional long-range structural organization.

1. Introduction

A salt in the liquid state below the temperature of 100°C is conventionally called an Ionic Liquid (IL). From a general point of view a *room-temperature ionic liquid* (RTIL) is a substance made entirely by ion pairs with a melting point below the 100°C. Some specific properties[1] of these materials, such as low volatility and thermal stability, made them an interesting subject of research due to the increasing number of possible technological and industrial applications[2-5]. Moreover, their low environmental impact

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makes them an optimal candidate as a new less harmful solvent in industrial processes. Given the huge number of anion-cation combinations, the possibility of providing RTIL with specific properties such as biocompatibility has opened new routes in the application of these material in the pharmacological and biomedical fields and, in general, in green-chemistry processes[6-9]. In this respect a new generation of ILs have been synthesized in which the classical inorganic anions such as $[PF6]^-$, $[BF4]^-$, Br^- , Cl^-, have been substituted by organic amino acid anions[10].

In this work we focus on this new set of ILs consisting of a choline cation $[Ch]^+$, mixed with various amino acid anions[11]: alanine $[Ala]^-$, valine $[Val]^-$, isoleucine $[Ile]^-$, norvaline $[Nva]^-$, norleucine $[Nle]^-$, leucine $[Leu]^-$, phenylalanine$[Phe]^-$, histidine$[His]^-$, proline $[Pro]^-$, cysteine $[Cys]^-$, threonine $[Thr]^-$.

This class of RTILs, given that both constituents play a role in metabolic processes, was proven to be non toxic for the humans and for the environment[12-14], and can be considered a promising class of materials for a large range of bio-related applications[15-17].

In this paper we present a systematic study of the structural properties for the series of the above RTILs, by using a powerful theoretical approach such as *ab-initio* molecular dynamics (AIMD) and by validation with accurate experimental measurements of their internal structure. The main objective of this work is therefore that of characterizing these materials by observing their nanoscopic structure.

In all the RTILs, the competition between the electrostatic forces that tend to form a lattice and the intrinsic disorder due to the bulky molecular components gives rise to a typical structure that has been elucidated in the (very rich) past literature. These materials are generally characterized by an alternating pattern of anions and cations that is reminiscent of a crystalline environment typical of solid salts. However this alternating pattern of ions is only transient, due to the inability of the electrostatic interaction to produce an ordered phase. This inability is due to the fact that the charge is delocalized over bulky molecular structures and lattice formation is heavily frustrated. Despite the intrinsic disorder of their liquid phase, it is well known that nanoscopic range ordering and complex aggregational structures may arise due to the peculiar substituent that can be inserted by organic synthesis to the polar component of the molecular ions and that

provide a mean to lend them amphiphilic character. As we shall see below, this is indeed the case of the $[Ch]^+[Phe]^-$ IL that shows long-range aggregation and an emerging peculiar structural organization for the stacking/aggregation of phenyl rings.

2. Methods

In order to provide a full characterization of the structure of the liquid within the relevant range of radial distances that are accessible to our experiments, we have performed different AIMD simulations of the bulk system composed by an equal number of amino acid anions ($[Ala]^-$, $[Val]^-$, $[Ile]^-$, $[Nva]^-$, $[Nle]^-$, $[Leu]^-$,$[Phe]^-$,$[His]^-$, $[Pro]^-$, $[Cys]^-$, $[Thr]^-$) and $[Ch]^+$ cations. A pre-equilibration was performed employing classical molecular dynamics within periodic boundary conditions, using the AMBER program package[18] and the Gaff force field[1920]. The partial atomic charges have however been recomputed owing to the RESP method using the B3LYP electronic density and the latter have been scaled by 0.8 to roughly account for polarization effects. Pre-equilibration took 1 ns of physical time and the simulation temperature was set at 350 K. The starting configurations yielded by this procedure were used to setup *ab-initio* molecular dynamics simulations with the program package CP2K[21], using the Quickstep module[22] and the orbital transformation[23] for faster convergence. The electronic structure was calculated by means of the PBE[24] functional, with an explicit Van der Waals correction that includes the empirical dispersion correction (D3) by Grimme[25]. Basis sets of the kind MOLOPT-DZVP-SR-GTH and GTH pseudopotentials[2627] were used. The timestep was chosen to be 0.5 fs and the simulation temperature was set to 350 K using the Nose-Hoover thermostat[28] in order to slightly accelerate the dynamics which is very slow at ambient conditions due to the high viscosity of these systems[11]. The cell side-lengths, and other simulation details are reported in Table S1 in the supplemental material[29] with the respective densities. For all the molecular combinations, the simulations have been conducted using unitary cells that contained from 10 to 15 ionic couples and whose side lengths were between 15 and 17 Å. For 5 selected amino-acid ions ([Ala], [Pro], [Phe], [Cys] and [Thr]), we have also performed the AIMD in a larger cell with 45 to 56 ionic couples and side lengths of about 25 Å to explore further distances. In this way, with a larger box edge, it is possible to perform a reliable comparison between theoretical and

experimental structure functions (see below). The total production simulation time generally exceeded 50 ps (see the simulation times in Table S1) for the small cells and was slightly less for the large cell systems. The trajectory post-processing and the investigation of structural properties have been carried out with the TRAVIS package[30] and "in house" software codes.

For the synthesis of the [Ch][AA] ILs, we used, with slight variations, the method recently reported in the literature by our group[31]. [Ch][OH] aqueous solution (about 2.5 M) was titrated by adding small amounts of solid AA under stirring at about 3 °C. In the proximity of the equivalence point each AA addition was reduced to about 1 mol% of the stoichiometric amount required for titration and excess of about 10-15 mol% of AA was added in order to better the equivalence point. The excess of AA was back titrated by adding the proper volume of [Ch][OH] with the same concentration of the starting [Ch][OH] solution. Water was then removed under reduced pressure at 50 °C. The product was dried *in vacuo* for 24h at 50 °C under stirring. The water content of all amino acid ionic liquids, determined with a Karl Fischer moisture titrator (831 KF Coulometer Metrhom), was less than 0.2 wt%.

The large angle X-ray scattering experiments were performed at room temperature using the non commercial energy-scanning diffractometer built in the Department of Chemistry at the University 'La Sapienza' of Rome (Italian Patent No. 01126484-23 June, 1993). For a detailed description of instrument, technique, and the experimental protocol of the data acquisition phase, the reader is referred to refs. [32333435]. In this experiment, the new $0 - 2\theta$ instrument geometry (only one of the two diffractometer arms can move) was used; the samples were prepared and put in 2-mm quartz cylindrical capillaries, immediately after a 72-h drying in high vacuum pump. In such setup, higher diffracted intensities can be recorded. The diffraction patterns acquired at the different angles were then joined to obtain a continuous spectrum in Q; only five diffraction angles are enough to cover a Q-spectrum ranging from 0.1 to 19.56 $Å^{-1}$.

3. Discussion

As discussed in the introduction AIMD simulations have been carried out for eleven ionic liquids consisting of a choline cation ($[Ch]^+$) with different amino acid anions: alanine $[Ala]^-$, valine $[Val]^-$, isoleucine $[Ile]^-$, norvaline $[Nva]^-$, norleucine $[Nle]^-$, leucine $[Leu]^-$, phenylalanine $[Phe]^-$, histidine $[His]^-$, proline $[Pro]^-$, cysteine $[Cys]^-$, threonine $[Thr]^-$. Though these are well known molecules, the cation and anion structures are reported in Figure S1 in the supplemental material[29]. In order to help the following discussion we plot in Figure 1 a generic scheme of the compounds that compose the liquids where the amino acid is in its deprotonated form.

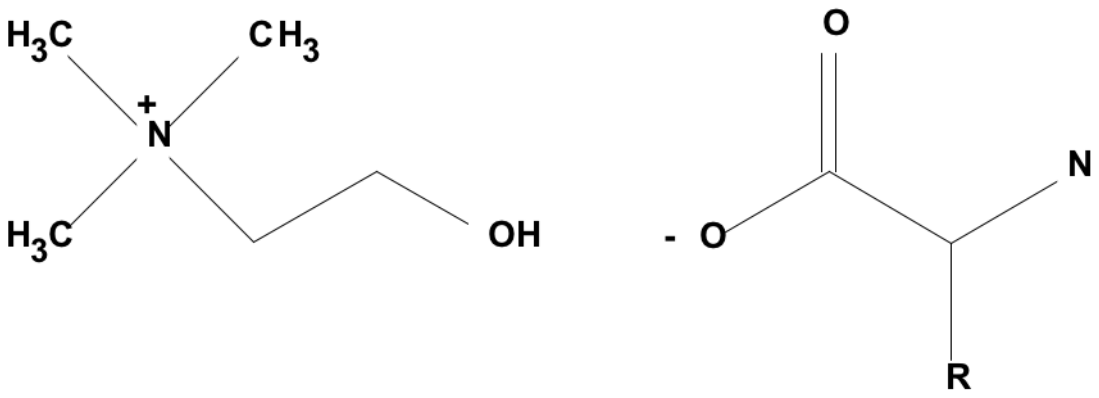

Figure 1: Scheme of the molecular components of the liquids under study: Choline cation on the left and the amino-acid anion on the right.

We have already provided in ref.[36] a preliminary study of the above compounds by focusing on their docking morphology for the isolated ionic couples in the gas phase. The results from a series of high quality *ab-initio* simulations have clearly shown that the docking geometry of the compounds behaves in a very similar manner along the entire series. The main bonding feature is a strong hydrogen bond between the OH group on $[Ch]^+$ and the carboxyl of the amino acid. This bonding feature represents substantially the driving force of aggregation beyond the obvious electrostatic cohesive force. We have however also discovered that the nanoscopic morphology at the molecular level is also driven by a weaker, but nonetheless persistent, interaction between the N^+ atom on $[Ch]^+$ with the negatively charged head of the amino acid anion. This doubly coordinating

feature makes the single ionic couple in the gas phase tightly bound to such an extent that this binding pattern survives in the liquid phase and is substantially representative of the local molecular geometry of the liquid. These important results have been further confirmed in a second study by us[37] that focused on the behavior of the compound [Ch][Ala] in the liquid phase through *ab-initio* and classical MD.

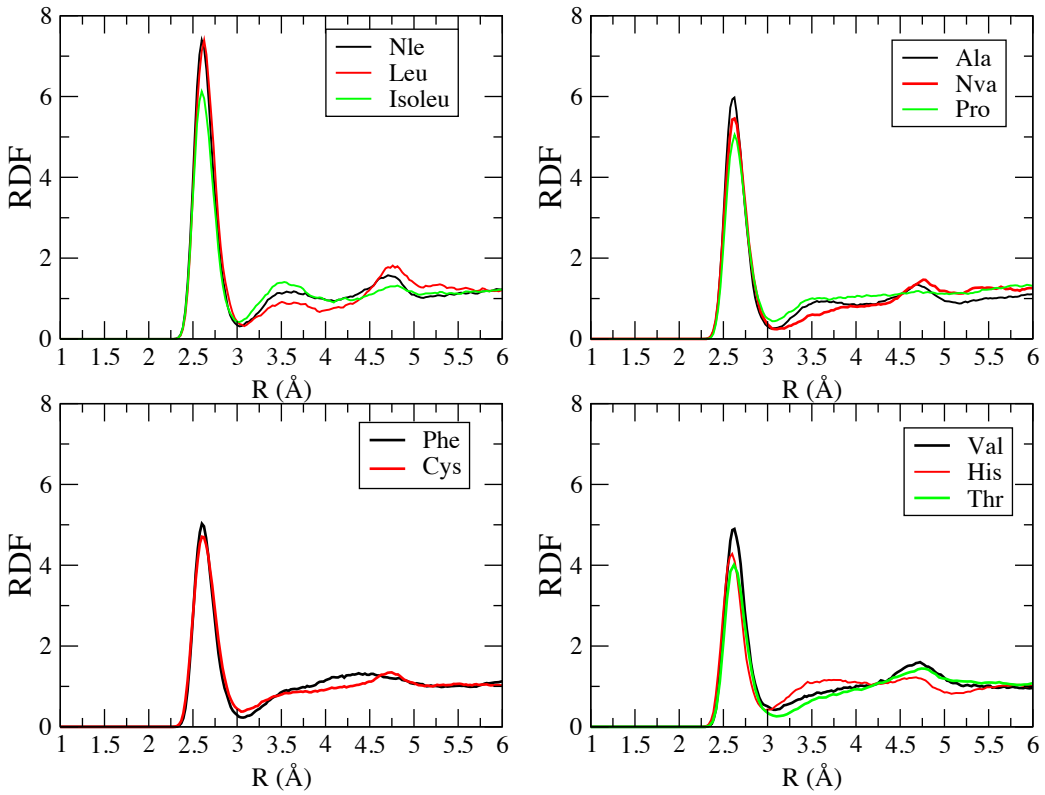

Figure 2: Oxygen-Oxygen intermolecular RDF.

In order to investigate the morphology (at least the short range one) of the entire series of compounds we have calculated the radial distribution functions (RDFs) between the most representative atoms of the $[Ch]^+$ cation and the amino acid anions in order to explore the short-range geometrical features. In particular, in Figure 2, we show the RDFs between the oxygen atoms of the cation and the oxygen atoms of the anions. The entire series of compounds show a very similar profile of this RDF that is characterized by a very clear and sharp peak due to the H-bonding at distances around 2.6 Å. The most intense peaks

in the O-O RDF are those of the various leucine amino acids while the least intense ones are those arising in the $[Cys]^-$, $[His]^-$, $[Val]^-$ and $[Phe]^-$. This peak is symmetric around its maximum thereby signaling a very strong H-bond in which the proton is exclusively localized on the $[Ch]^+$ cation. The acceptor-donor distance is in line with those that we already had found in the gas phase isolated ionic couples that turned out to be in the 2.6-2.7 Å interval. These results confirm that the hydroxyl group of the cation interacts with the carboxylate group of the anions reaching an O-O equilibrium distance in agreement with the presence of a strong H-bond. Obviously, since one of the two oxygen atoms of the carboxylate is involved in a strong H-bond, the second is located at a fixed distance from the first, giving rise to the second peak in Figure 2 between 3 and 4 Å. This shows again that the structure of the liquid is determined by the intra-ionic couple interactions and that the alternating pattern of cations and anions persists in the liquid phase with a local geometric arrangement that is reminiscent of the gas phase[36].

We can see a further confirmation of the above conclusion by looking at the N-O intermolecular RDF which we show in Figure 3. The reported RDF show clearly how, even in the liquid phase, the much weaker interaction between the positively charged head of the $[Ch]^+$ cation and the negatively charged carboxyl oxygen survives and acts a as a docking force, in turn, determining the local morphology of the ion-ion interaction.

We report in Table 1 some of the geometric parameters that characterize the ionic couples. We also report the running volumetric integral of the RDF (sometimes called coordination number) for both the O-O and the N-O RDFs in Figure 2 and Figure 3. As we can see the O-O coordination number is almost one in all liquids so that we do not expect the cations (which are the hydrogen bonding donors) to form more than one hydrogen bonding for each ion pair. The coordination number for the O-N case is instead fluctuating between 4.5 and 5. Since the positively charged head of the [Ch]+ ion can coordinate up to almost 5 negatively charged oxygen atoms, we conclude that this interaction coordinates more than one, possibly two, anions to a single cation.

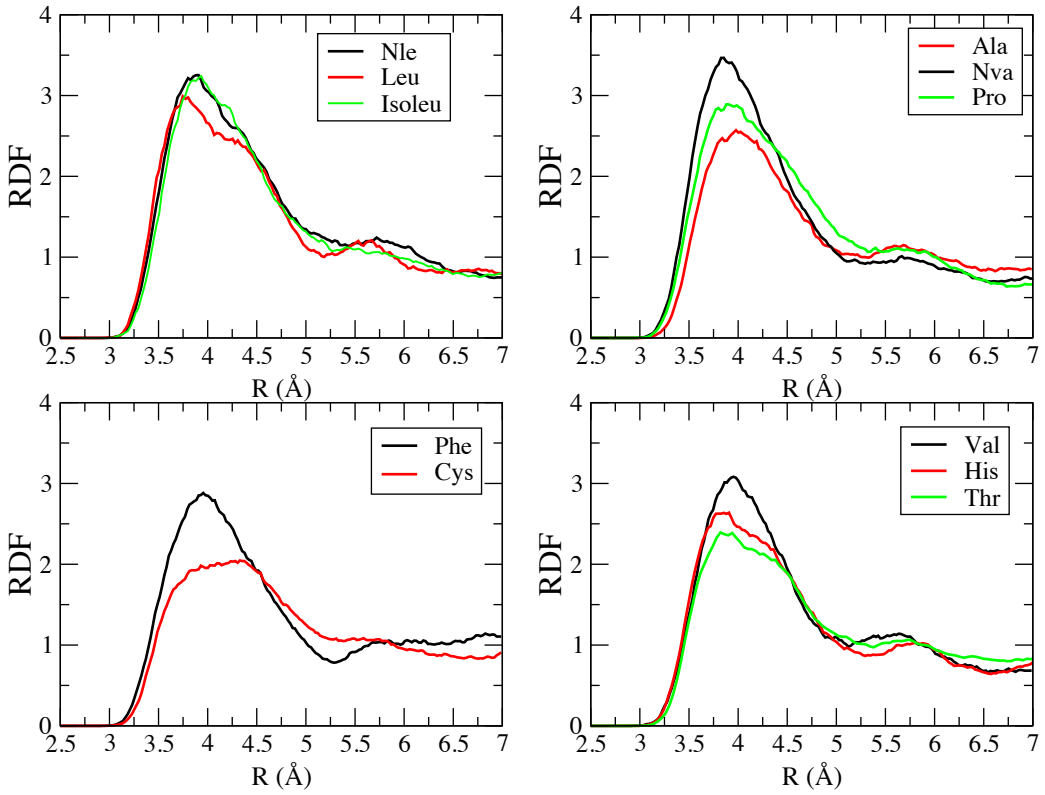

Figure 3: O-N intermolecular RDF

	[Nle]⁻	**[Leu]⁻**	**[Ile]⁻**	**[Ala]⁻**	**[Nva]⁻**	**[Pro]⁻**	**[Phe]⁻**	**[Val]⁻**	**[Cys]⁻**	**[Thr]**	**[His]⁻**
O_{an}-O_{ch} (Å)	2.60	2.62	2.60	2.62	2.63	2.63	2.60	2.63	2.60	2.62	2.60
N_c (3 Å)	0.90	0.95	0.79	0.96	0.73	0.78	0.68	0.77	0.89	0.66	0.63
O_{an}-N_{ch} (Å)	3.90	3.75	3.93	3.97	3.85	3.88	3.95	3.95	4.33	3.87	3.91
N_c (5.2 Å)	4.76	4.48	4.61	4.80	4.55	5.08	4.32	4.96	4.76	4.07	4.40

Table 1: Geometric features of the liquids. Nc in third and fifth rows is the value of the running volumetric integral of the RDF, i.e. the coordination number.

Furthermore, as we can see in Figure 3 the $[Ch]^+[Cys]^-$ N-O RDF shows a less intense and structured peak. This feature can be explained as an effect of the competition between the O_{cys} and S_{cys} involved in the electrostatic interaction with the N_{ch} of the cation. Indeed the RDFs between N_{chol} and O_{cys} and N_{chol} and S_{cys} have been compared in Figure 4 where we can see a well-defined RDF between N_{chol} and S_{cys} which confirms our hypothesis and localizes the sulphide terminal at around 5 Å from the $[Ch]^+$ cation.

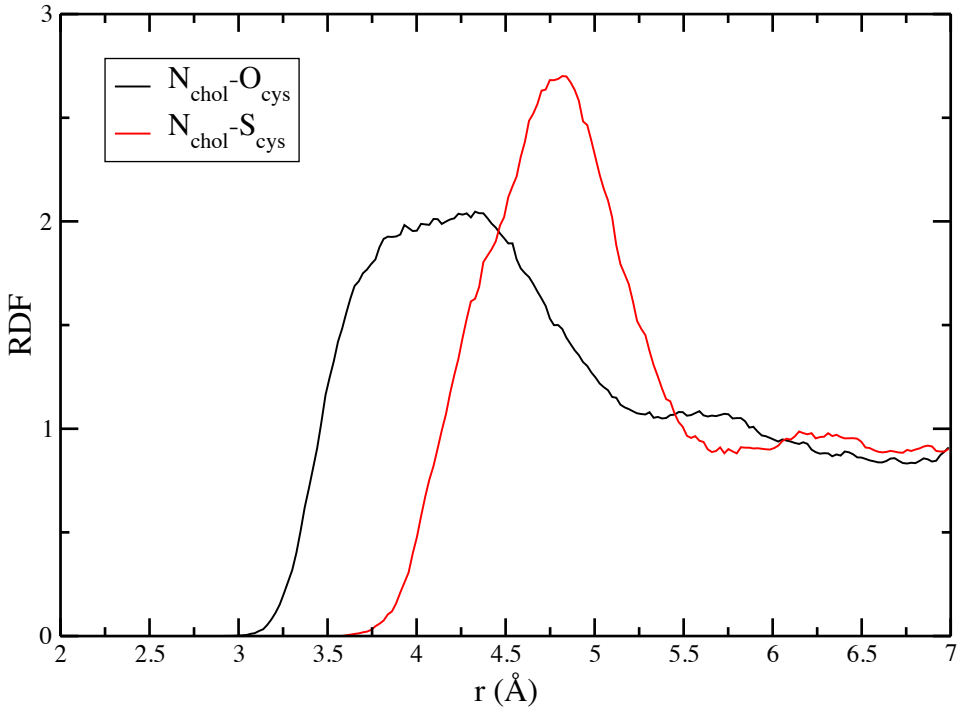

Figure 4: N-O and N-S RDF for the [Ch][Cys] liquid.

In addition to the atomic RDF we have also calculated the radial distributions between the center of mass for the cation-cation, anion-anion and anion-cation combinations. In order to provide meaningful results and due to the size of the molecular constituents these quantities have been computed only for those liquids for which we have a simulation with

a sufficiently large cell sizes i.e. for the systems composed by choline and $[Ala]^-$, $[Cys]^-$, $[Pro]^-$, $[Phe]^-$ and $[Thr]^-$.

The cation-anion RDFs, in Figure 5 show a broad first peak around 5 and 6 Å confirming again that each ion with a given charge is systematically surrounded by ions of opposite charge. The cation-cation, and anion-anion RDFs (not reported) are less structured and their main peak appears at larger distances than that of the cation-anion RDF as can be seen in Figure 6.

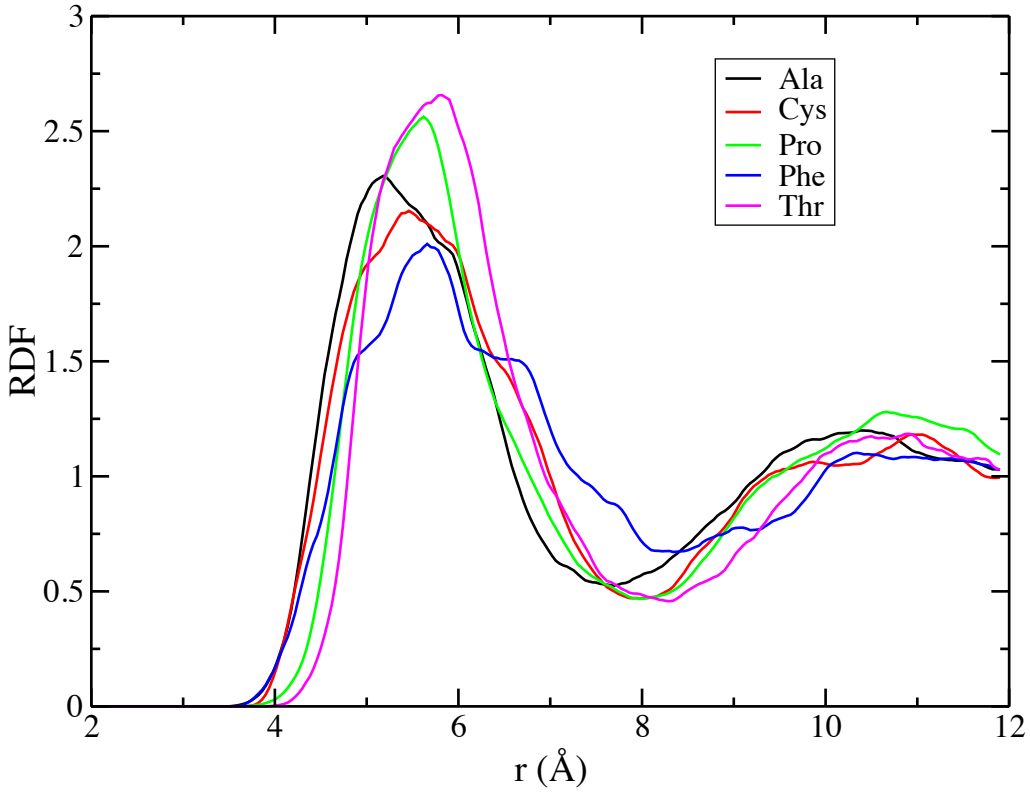

Figure 5: Center of mass RDF between cation and anion.

All ionic liquids show the same general features except for the $[Ch]^+[Phe]^-$ system where the cation-cation RDF in Figure 6 shows a unique feature around 5 Å beside the common maximum at 6 Å. This emerging feature suggests a possible further structural organization for this IL.

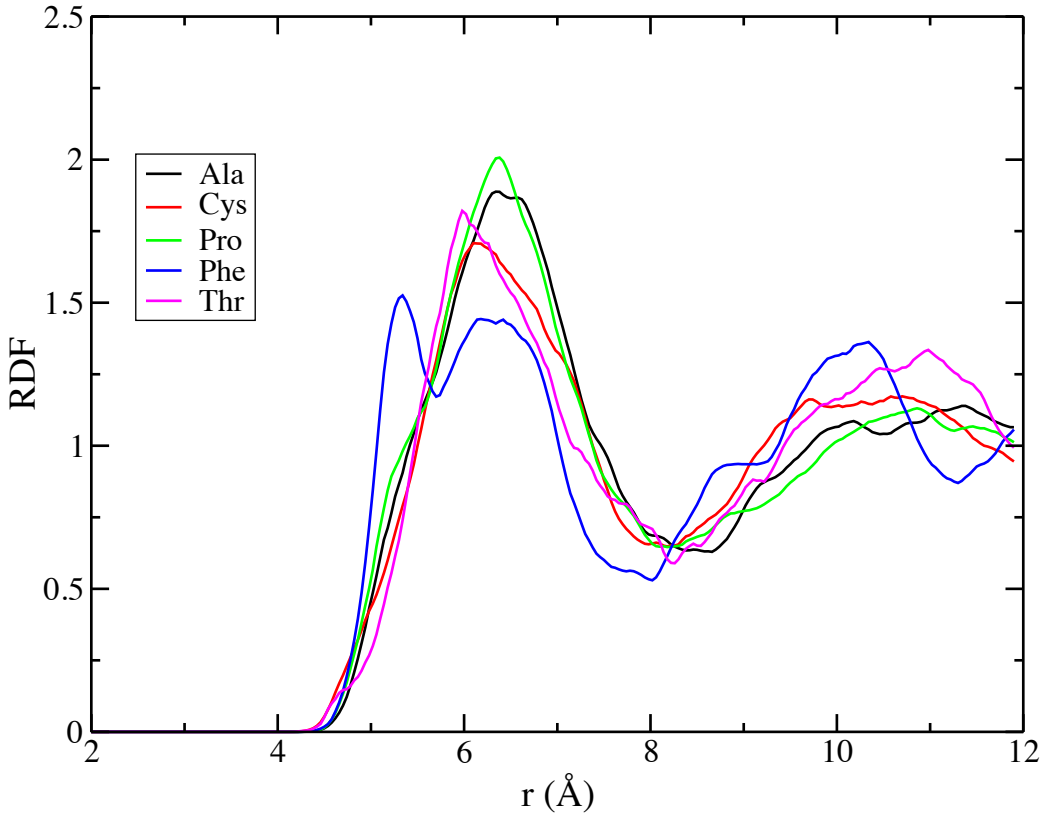

Figure 6: Center of mass radial distribution function between cations.

In this respect, the center of mass RDF of the phenyl-phenyl has been calculated in order to investigate the possible effect of phenyl-phenyl stacking. As we can see in Figure 7, a recurring pattern of peaks in the relevant RDF between the ring centers might suggest the occurring of phenyl stacking on the long range. This kind of interaction might be at the basis of the unexpected behavior of analogous systems where long range aggregation phenomena have been measured. [38]

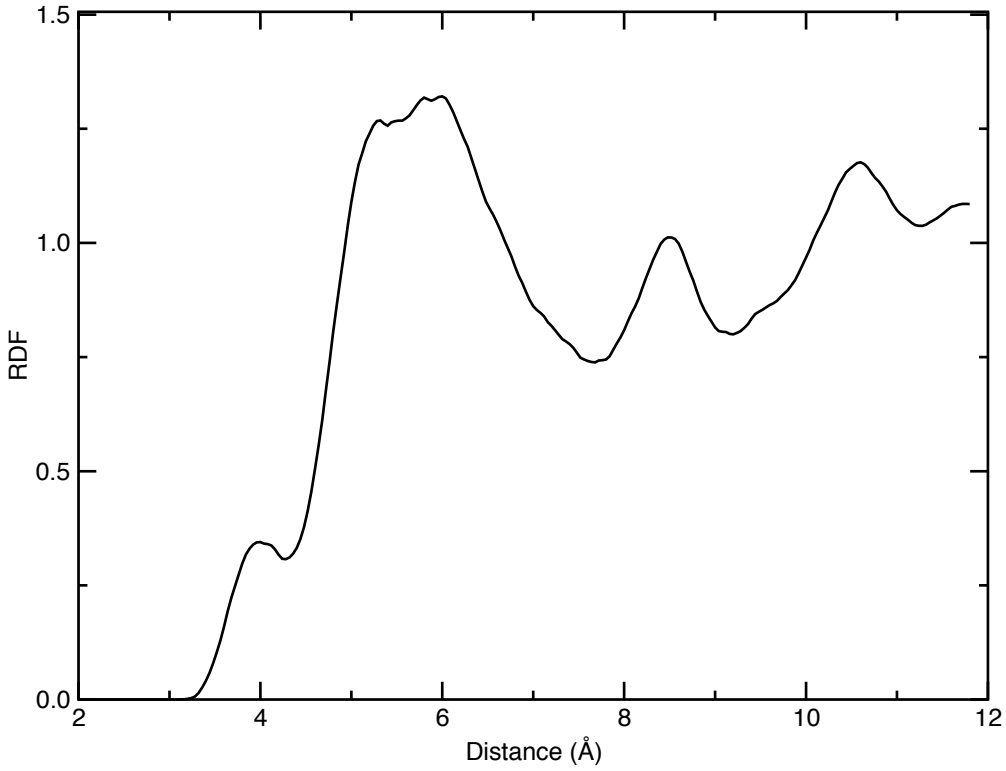

Figure 7: RDF between the phenyl rings centers in the [Ch][Phe] compound.

Some illustrative snapshot of the anion-anion and cation-cation interactions are reported in Figure 8 where the presence of a stacking organization between the phenyl rings should be clear.

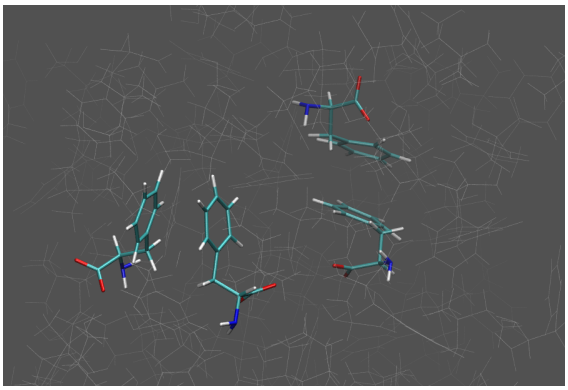

Figure 8: Snapshot of trajectory: Phenyl-Phenyl interaction;

A particular feature concerns the [Ch][Cys] RTIL: during the analysis of the trajectory we have realized that an intra-molecular proton transfer (from the SH group to the NH_2 group) was observed in two cysteine molecules that therefore appeared as anions in an anionic-zwitterionic form $[S^-$ --R--$NH_3^+]^-$. In order to understand this effect, DFT calculations in gas-phase have been performed on isolated cysteine in anionic and anionic-zwitterionic form, comparing their thermodynamic stability. The structures are reported in Figure S2 in the supplemental material[29]. The calculations have been performed with 3 different functional: B3LYP, CAM-B3LYP, ω–B97XD, and PBE using a 6-311G* basis set. According to the results reported in Table 2, the anion cysteine monomer in anionic-zwitterionic form (anion_ZW in table) is found between 2 and 4 kcal/mol less stable than the normally charged monomer ref [39]. It is however very likely that the highly ionic environment of the liquid can lower this energy difference therefore making the appearance of the anionic-zwitterionic form more likely. This fact alone should clearly show how difficult and prone to errors can be the study of such materials with classical methods of molecular dynamics where the topology of the partner ions is decided once and conserved along the system evolution. Especially in the case of highly protic ionic liquids such as [Ch][Cys], the possibility of proton transfer should be taken into account. Proton transfer phenomena seems to be not present (at least in the time span of our simulations) in all the others ILs examined here so that the classical molecular dynamics reported by us in Ref. [37] should retain its validity.

	ΔE (kcal/mol) B3LYP	**ΔE(kcal/mol) CAM-B3LYP**	**ΔE(kcal/mol) ωB97XD**	**ΔE(kcal/mol) PBE**
Anion_ZW	4.42	4.90	4.54	2.28

Table 2: Energy difference of the Anion ZW form with respect to the Anion one. Calculations performed with 6-311G basis set.*

4. The X-ray structure factors

We conclude this work by presenting a comparison of the calculated X-ray static structure factors with available experimental data. An overview of the methods and of the formula used can be found in the supplemental material[29] and in Ref. [37] where an analogous comparison has been carried out for the [Ch][Ala] compound. The resulting structure factors have been obtained only for the compounds for which we had a sufficiently large cell given that its size governs the maximum extent of the interatomic RDFs that have to be used to calculate the reciprocal space functions.

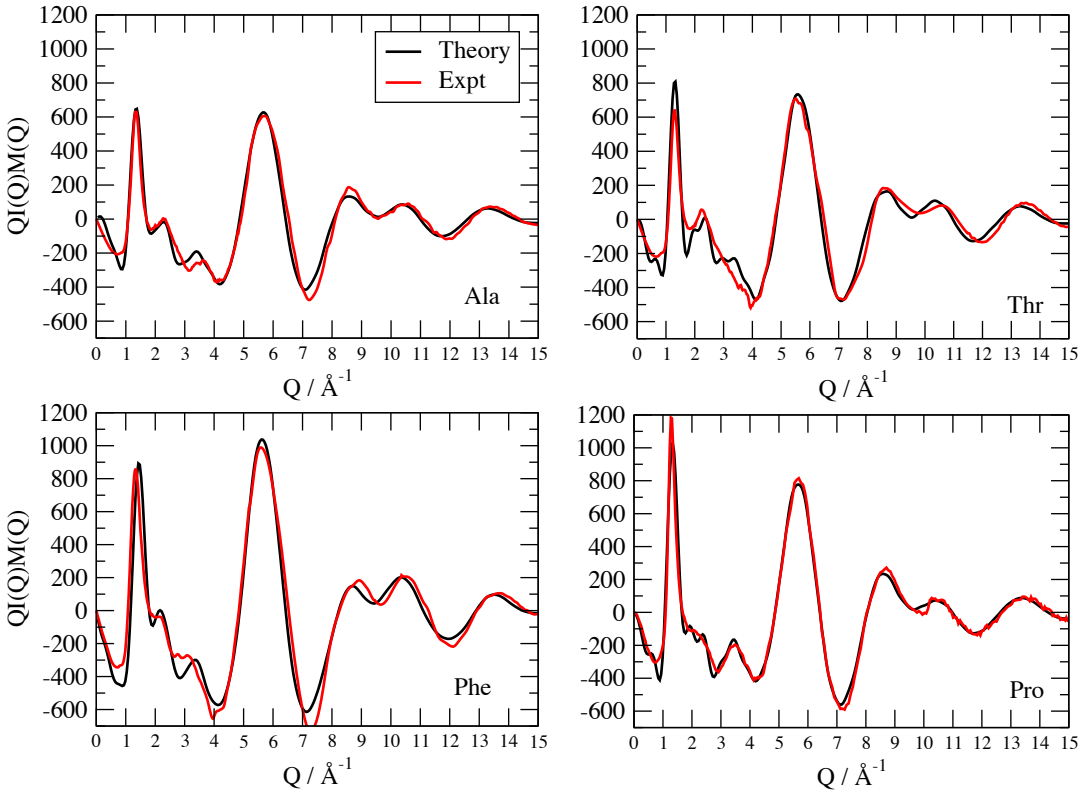

Figure 9: Calculated (black) and experimental (red) X-ray static structure factors.

The results are presented in Figure 9 where we report the *QI(Q)M(Q)* quantity (see the supplemental material[29]). As can be easily seen, the agreement between the calculated and experimental diffraction patters is excellent on the relevant scale of distances involved. It is important to point out that the theoretical data below 0.5 Å^{-1}

are unreliable due to the finite size of our simulation cells. The interpretation of the diffraction patterns is not easy given that the experimental data is mediated over all the configurations of all the inter-atomic distances. Anyway we can easily recognize two regions in the above patterns that correspond roughly to the intramolecular distances above 5 $Å^{-1}$ and to the intermolecular distances below this value. As we can see, the agreement in the intramolecular region is excellent and is certainly due to the accuracy of the *ab-initio* computation of the forces. The agreement is also very good (both in terms of position and height of the peaks) for the intermolecular region below 2.5 $Å^{-1}$. In this region we find the principal peak that falls between 1 and 2 $Å^{-1}$ and that correlates with distances that are between 3 and 6 Å. This peak is due to the alternating pattern of cations and anions in the liquid and represents a clear fingerprint of the local structure of RTIL in general. The shoulder appearing at the right of the main peak around 2.2-2.4 $Å^{-1}$ is mostly due to the O-O correlation due to hydrogen bonding whose peak falls at 2.6 Å in the direct space. The third peak between 3 and 4 $Å^{-1}$ (which is almost invisible for the $[Thr]^-$ anion) already falls at distances in the direct space (1.8 Å) that can be due to both inter- and intra-molecular distances and is difficult to interpret properly.

5. Conclusions

We have reported for the first time a comprehensive *ab-initio* study of the local morphology of a homologous series of ionic liquids based on amino acids anions and the cholinium cation. The data have been obtained with *ab-initio* molecular dynamics using the PBE pure functional in conjunction with the long range van der Waals corrections. The accuracy of our computations has been tested against high quality experimental X-ray diffraction patterns. The agreement with the experimental data is excellent on a wide range of distances and validates our approach to structural analysis. The homologous series of 11 compounds analyzed here presents general and persistent structural motifs that characterize all compounds. In particular we have found that the liquid structure is substantially built out of two main docking interactions that act between the differently charged ions: the first one is a strong hydrogen bonding feature that connects the carboxyl

terminal of the amino-acids anions to the hydroxyl group of the cation. The hydrogen bonding interaction leaves the charged head of the $[Ch]^+$ cation, that is represented by the quaternary nitrogen atom, free to form a secondary, albeit still important, interaction with the carboxyl oxygen atoms. While the hydrogen bonding feature tends to connect directly a single cation to a single anion, the N(+)-carboxyl interaction provides a network that pervades the liquid and connects each cation to more than one anion. Peculiar structural features have been detected for the [Cys] and the [Phe] anions: in the former an intramolecular proton transfer from the S-H group to the NH_2 one leads to the formation of a zwitterionic species; the latter has shown to possess an additional peculiar structural organization that is due to phenyl ring stacking and that leaves a clear imprint in the radial distribution profile.

Acknowledgements

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