



# Choline-amino acid ionic liquids: past and recent achievements about the structure and properties of these really “green” chemicals

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## Abstract

The structure of choline-amino acid ionic liquids, atoxic task-specific solvents composed of materials originated from renewable feedstocks, is reviewed in this letter. The varied and strong interactions that these liquids are capable of establishing are largely dependent on their structure and confer them outstanding solvating properties with respect to a large number of different solutes. Among the experimental methods capable of yielding structural insight, the energy-dispersive version of X-Ray diffraction, that uses the Bremsstrahlung radiation of the X-Ray tube, is a technique very well suited to investigate these liquid systems. The diffraction spectra of five choline-amino acid ionic liquids, recently measured, are reported and discussed; in particular, the presence or absence of the medium-range order pre-peak is related to the presence of polar groups within the amino acid side chain that destroys the hydrophobic interactions between aliphatic chains. In the final section, a recent example of choline-amino acid ionic liquids as for ancient paper preservation and two other interesting results are discussed at the end.

**Keywords** Choline-amino acid ionic liquids · EDXD · Ion pairs · Pre-peak · Renewable materials

## Introduction

Since choline-amino acid ionic liquids (ChoAA-ILs) were introduced in 2012 by Liu et al. (Liu et al. 2012), the interest in these systems obtained from natural and renewable feedstocks has increased significantly, as witnessed by the large number of papers appeared in the last few years, and some new fields of application have been opened. Indeed, though the use of ChoAA-ILs in the field of biomass processing for which they were originally developed—they possess the amazing property of solubilizing lignin selectively from rice straw—has steadily continued to grow (Hou et al. 2013b; Reddy 2015; Wang et al. 2016; To et al. 2018), the powerful solubilization properties of these liquids were extended to other systems, like drugs (Alawi et al. 2015), to the extraction of noxious

substances in cigarette smoke (Zhang et al. 2016), and to lignite and thermal coal pre-treatment (To et al. 2017). In addition, these compounds have found use as lubricants (Mu et al. 2015; Jiang et al. 2018; Zhang et al. 2018; Wu et al. 2018), as CO<sub>2</sub> capture agents (Zhang et al. 2013; Bhattacharyya and Shah 2016; Saptal and Bhanage 2017), and as antimicrobials (Foulet et al. 2016), in topical formulations for drug delivery (De Almeida et al. 2017), and they have shown to possess selective antiproliferative activity against some breast cancer cell lines when complexed with hemocyanins (Guncheva et al. 2015). Probably, the most striking feature of ChoAA-ILs lies in the fact that this variety of properties goes along with their substantial harmlessness. Indeed, they are considered not harmful for marine organism (Baharuddin et al. 2016), as well as largely biodegradable (Hou et al. 2013a; Yazdani et al. 2016; Foulet et al. 2016) and atoxic (Zhang et al. 2018), though one study reported toxicity with respect to some marine bacteria (Ventura et al. 2014). On the contrary, one of the greatest limits to their technological application is the very high viscosity of the liquid phase (De Santis et al. 2015; Bhattacharyya and Shah 2016). All these properties are deeply rooted in the various structural motifs that ChoAA-ILs display.

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## Structural features

A ChoAA ionic liquid is basically composed of the quaternary ammonium cation choline (N,N,N-trimethylethanolammonium or 2-hydroxy-N,N,N-trimethylethan-1-aminium, according to IUPAC nomenclature) and of an amino acid anion ( $\text{NH}_2\text{-CHO(R)-COO}^-$ ), like glycinate and lysinate (see Fig. 1).

These two charged groups are different in nature. In the cation, the analysis of the electrostatic potential, calculated from the electron distribution originated from the wave function and from the nuclear charges, states that the positive charge of the cation is located on the three methyl(ammonium) group hydrogen atoms, on the nitrogen atom, and on the terminal hydroxyl hydrogen (OH). The large N-(CH<sub>3</sub>)<sub>3</sub> fragment, given its large extension and consequently not dense charge, is “soft” and polarizable, while only the OH moiety is highly polar. In the anion, instead, the charge is more densely localized in the carboxylate group (COO<sup>-</sup>), while most amino acid side chains have little polar character. Carboxylate can also act as hydrogen bond acceptor, while choline hydroxyl group can be both hydrogen bond donor and acceptor; other H bond active groups can be found in the side chains of polar amino acids (e.g., serine, glutamic acid). Further possible interactions include cation- $\pi$  and  $\pi$ - $\pi$  stacking that are carried out by the aromatic moieties of amino acids (phenylalanine, histidine). It comes as no surprise, therefore, that all these available interaction patterns provide ChoAA-ILs with large solvating power for a wide variety of different substances. Yet, the downside of such power is the very strong association between the ions that make these systems often extremely viscous as well as non-conductive, since the mobility of the charge carriers (ions) is heavily hindered. A thorough description of the correlation between experimental properties, such as density, viscosity, conductivity, refractivity, and amino acid type in ChoAA-ILs, is given in De Santis et al. paper (De Santis et al. 2015). In the study, for instance, the maximum “hindering effect” is reported for choline-histidine, where all types of interactions come into play. In the same study, the authors report as well an innovative synthesis method, based on a potentiometric back-titration of the excess reagent choline oxide, instead of the simpler method (Liu et al. 2012; Tao et al. 2013). The presence of such strong interaction between the ions was later supported by several theoretical and experimental studies that have pointed out that ion pairing, strengthened by the hydrogen bond interaction between carboxylate and hydroxyl groups, has a prominent role among the interactions described. Regarding theoretical

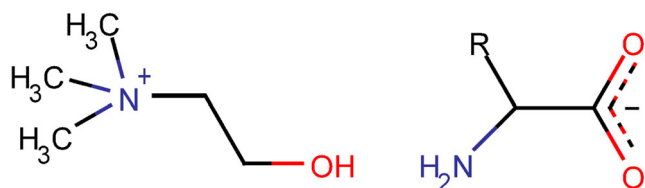


Fig. 1 Structural formula of choline-amino acids in general

studies, some first-principle calculations, that are unbiased on point charge representation, confirmed the existence of a strong and stable ion pair. In the first investigation, Benedetto et al. (Benedetto et al. 2014) described in detail the cation-anion interaction with DFT methods in vacuo and in small clusters containing up to four ion pairs, for eight amino acid anions (Ala, Val, Ser, Cys, Asp, Asn, Phe, His). In some later reports (Campetella et al. 2015a, b, 2016a, b, c, 2017, 2018), the presence of strong ion pairing was confirmed in larger models of the liquid phase (32 ion pairs). In one of these studies on choline-alanine (Campetella et al. 2015a, 2015b), infrared spectroscopy was chosen as experimental technique to support the computational results. The huge red shift ( $\Delta\nu=900\text{--}1000\text{ cm}^{-1}$ ) of hydroxyl stretching vibration observed in the experiment was correctly reproduced by the model and was interpreted by calculating the Wannier centers along the AIMD trajectory, as due to the large number of different conformations and energies experienced during the simulation by the hydrogen bond-mediated pairs. The shifts induced in infrared spectra were also recognized in the similar family of ionic liquids, choline-carboxylic acids that share the same structural ion-pairing motif. In the experimental/theoretical works by Tanzi and coworkers (Tanzi et al. 2014) that contain IR/RAMAN spectra and calculations, the authors report a redshift of about  $200\text{ cm}^{-1}$  for carbonyl stretching vibration and for carbonyl torsion and of about  $700\text{--}800\text{ cm}^{-1}$  for hydroxyl stretching; interestingly, the hydroxyl shift is reduced to  $600\text{ cm}^{-1}$  when competing intramolecular OH $\cdots$ O interactions are possible, like in salicylate anion (Tanzi et al. 2016). Besides infrared spectroscopy, another technique able to point out the interaction occurring in the system is liquid X-Ray diffraction, particularly in the energy-dispersive variant, energy-dispersive X-Ray diffraction (EDXD). Examples of applications to liquids can be found in Gontrani et al. 1999, 2008, 2009. Although the results it can give are not focused on the specific interaction, like vibrational or magnetic resonance spectroscopies, diffraction can give a general picture of the molecular packing of the liquid phase. Several diffraction studies on ionic liquid morphology have pointed out the following aspects. First, when medium-range order (MRO) is present in the system, the diffraction patterns show typical features, termed pre-peaks or low-q peaks, that occur in the  $0.2\text{--}0.7\text{ \AA}^{-1}$  range (Greaves et al. 2010; Russina et al. 2012; Hayes et al. 2015; Campetella et al. 2015b) before the principal or main diffraction peak (“adjacency peak” in Kashyap et al. 2012). Medium-range order is usually defined as a structural correlation persisting in the range  $1\text{--}10\text{ nm}$  and is originated, in ILs, by the alternation of domains of different polarities. Secondly, when an extended hydrogen bond network permeates the liquid, some medium intensity peaks or shoulders appear in the  $2.5\text{--}3\text{ \AA}^{-1}$  range after the principal peak. The latter feature was pointed out for every ChoAA-ILs investigated and once again accounts for the strong ion-pair interaction, since it is mostly ascribable to the O–O correlation and has a counterpart in the total radial distribution

function, that is the Fourier transform of the diffraction pattern, where a peak falling around 3 Å appears. Regarding the former structural correlation (MRO pre-peak), it is widely accepted that alkyl chains linked to the central core of the ion tend to aggregate, forming, for instance, layers of interdigitated chains (Pontoni et al. 2017), sponge-like structures (Hayes et al. 2011), or similar arrangements, when the alkyl chain contains at least four carbon atoms. Indeed, the pre-peak was identified in ChoAA-ILs with at least four carbon atoms in the side chain (norleucine (Russina et al. 2016), norvaline (this work)), but also in choline-proline and choline-phenylalanine and in its non-proteinogenic derivative choline-homophenylalanine, as well as in leucine, isoleucine, and valine (this work). In these systems, the side chains are shorter than four carbon atoms, having one, two, and three carbon atoms, respectively. Concerning choline-proline (Campetella et al. 2015b), the morphology of the liquid was described as a collection of strong and quite rigid ion pairs (proline ring can be thought as a “cyclized” chain) that solvate each other, and the pre-peak observed at  $0.4 \text{ \AA}^{-1}$  results from the summation of positive contributions from like terms (cation-cation–anion-anion) and negative ones (unlike cation-anion terms), both originated from second-shell correlations at around 12.5 Å. In choline-phenylalanine and homophenylalanine systems, the experimental study (Campetella et al. 2015b) showed evident pre-peaks for both liquids that comply very well with theoretical patterns (Campetella et al. 2016a), obtained from a model where a relevant number of stacking interactions between phenyl rings were established, whose structural correlations take the place of the chain-chain interactions. The full list of the systems investigated with EDXD and the presence/absence of the pre-peak are given in Table 1, with proper referencing.

### Some examples of different ChoAA-IL EDXD patterns: going in deeper detail

In the following paragraph, the EDXD patterns measured for choline-valine, choline-norvaline choline-leucine, choline-isoleucine, and choline lysine are discussed. As anticipated, EDXD is a variant of X-Ray diffraction that exploits the dependence of diffracted intensity on the energy of the radiation, according to the definition of the scattering variable for the Compton scattering between a photon and an electron:  $q = \frac{4\pi\sin\vartheta}{\lambda}$ . This relation links the magnitude of the scattering variable (or momentum transfer) to the scattering angle ( $2\vartheta$ ) and to the wavelength of the incident radiation. Since the wavelength is related to the energy of the photon by the Planck equation  $E = h\nu$  ( $h = \text{Planck constant}$ ), we obtain  $q = \frac{4\pi\sin\vartheta}{hc} E \approx 1.014 E \sin\vartheta$ . Therefore, the whole spectrum of scattered wave vectors can be obtained either by varying the angle and keeping

**Table 1** List of ChoAA-ILs investigated with EDXD

System	Pre-peak	Reference
Cho-Gly	No	a
Cho-Pro	Yes	a, c
Cho-Leu	Yes	a, this work
Cho-His	No	a
Cho-Met	Yes	a
Cho-Phe	Yes	a, d
Cho-Ile	Yes	a, this work
Cho-Glu	No	R. Caminiti, private communication
Cho-Thr	No	a
Cho-Lys	No	a, this work
Cho-Val	Yes	a, this work
Cho-Ser	No	a
Cho-Trp	No	R. Caminiti, private communication
Cho-Cys	No	a, f
Cho-Nov	Yes	a, this work
Cho-Nor	Yes	a, e, g
Cho-Omo	Yes	a, d
Cho-Ala	No	a, b
Cho-Asp	No	a, f

a = De Santis et al. 2015; b = Campetella et al. 2015a; c = Campetella et al. 2015b; d = Campetella et al. 2016b; e = Russina et al. 2016; f = Campetella et al. 2017; g = Campetella et al. 2018

the radiation energy fixed (angular dispersive, ADXD, that uses a monochromatized beam) or by using a variable-wavelength energy beam (i.e., the “white” part of the radiation emitted by an X-Ray tube—Bremsstrahlung) and using a single angle or a limited number of angles (3 to 4). Several reviews on EDXD theory (Rossi and Caminiti 1999) and applications (Gontrani et al. 2014; Caminiti et al. 1997; Caminiti et al. 1999), to which the reader is referred to, were published in the past. After data treatment (see Gontrani et al. 2014) that normalizes the measured scattered intensity for absorption and subtracts self-scattering and the inelastic Compton scattering, the total coherent structure function, which is also known as “reduced intensity”,  $I(q)$ , is obtained.  $I(q)$  is the structural sensitive part of the recorded diffracted intensity, as it depends on the sum of the interference contributions of the waves scattered by the atoms of the sample, and, ultimately, on their relative distances, as the atoms, through their electrons, are the particles taking part to the scattering phenomenon (scatterers). From the Fourier transform of  $I(q)$ , the total radial distribution function of the sample is obtained. This is a “real” space (or “direct” space) representation of the scattering and is complementary to the  $I(q)$ , as the same structural features may give a strong signature in  $I(q)$  and a small

one in the radial distribution, and vice versa. It is important to note that the radial distribution is a function of the (relative) distance, while the “reciprocal” space  $I(q)$  depends on momenta that are inversely proportional to the distance (large distance = small momentum and vice versa). The functional form chosen for the total radial distribution functions shown in this work is the “differential” one ( $\text{Diff}(r)$ ), defined as:

$\text{Diff}(r) = D(r) - 4\pi r^2 \rho_0 = \frac{2r}{\pi} \int_0^{q_{\text{max}}} q I(q) \sin(rq) dq$ . In this expression, the non-structural term, due to the uniform radial distribution of particles that depends on the system density  $\rho$ , is left out.

In Fig. 2, the structure function  $I(q)$  of choline-leucine, multiplied by  $q$  and by a sharpening factor  $M(q)$ , is shown.  $M(q)$  is a mathematical function used to reduce the truncation error of the Fourier transform and to highlight the large  $q$  contributions. The following main features can be identified in the spectrum, going from low to high  $q$ :

- 1) The presence of a MRO-pre-peak at  $0.32 \text{ \AA}^{-1}$ , ascribable to a medium-range order structural correlation between the amino acid side chains and corresponding to an effective distance  $D_{\text{eff}} = 2\pi/q \approx 19.63 \text{ \AA}$
- 2) Main peak around  $1.3 \text{ \AA}^{-1}$ , mostly originated by all the intermolecular first-shell contributions
- 3) Small peak at  $2.31 \text{ \AA}^{-1}$ , corresponding to direct-space effective correlations falling at  $2.72 \text{ \AA}$ , sign of the strong cation-anion interaction through  $\text{O}\cdots\text{O}$  hydrogen bond distance
- 4) Molecular peaks at larger  $q$ , due to correspondingly shorter distances that reflect the conformational equilibrium of the molecule. When flanked by appropriate molecular modeling simulation, a detailed analysis of this

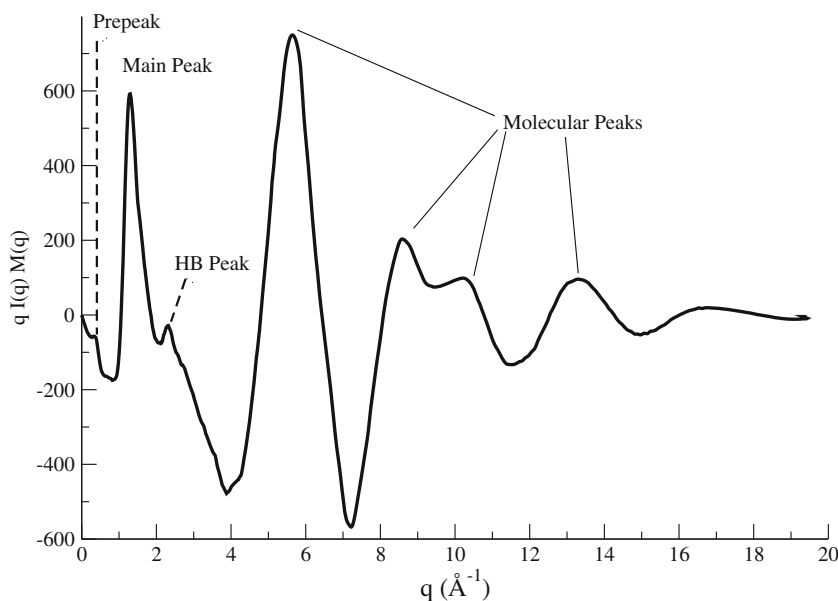
portion of the spectrum would give information about the population of the different conformers of the molecule (see, e. g. Campetella et al. 2016c, d).

The structural picture drawn by  $I(q)$  has the counterpart in direct space in the  $\text{Diff}(r)$  curve, shown in Fig. 3. In the picture, moving from small to large  $r$  values, the following interaction peaks can be highlighted:

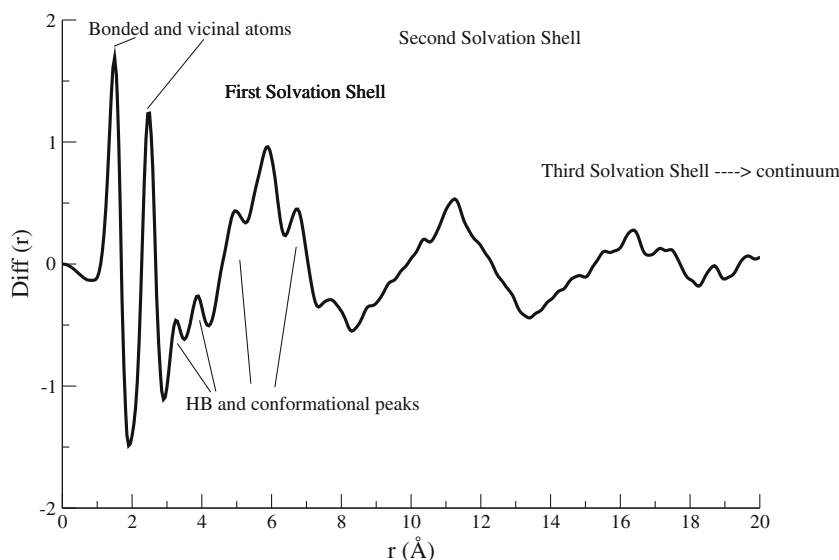
- 1) The first two molecular peaks are contributed by first- and second-neighbor contributions of bonded and vicinal atoms
- 2) Starting from  $3 \text{ \AA}$ , intermolecular interactions begin to occur and their peaks superimpose with the longer intramolecular peaks (for instance, end-to-tail distances of atom chains) that come out of the large bundle of first-shell intermolecular peaks that extends in the range  $3\text{--}8 \text{ \AA}$
- 3) Second and third solvation shell peaks, progressively broader and centered at about  $11$  and  $16 \text{ \AA}$ , are visible beyond, in compliance with the strong cohesion that make ionic liquids highly correlated liquids. The structural correlation is lost into statistical noise after  $18 \text{ \AA}$ .

When a comparison between different diffraction patterns within a family of compounds is needed, the most convenient way of expressing the structure function is the so-called atomic form ( $S(q)$  or  $F(q)$ ). In this formulation, the  $I(q)$  function is normalized by the non-structural contributions, i.e., the relative concentrations of the species ( $x$ ) and the scattering factors of the species ( $f$ ):  $S(q) = \frac{I(q)}{\sum x_i f_i^2}$ . In doing so, the functions can be directly compared; otherwise,  $I(q)$  intensities would be

**Fig. 2** Structure function  $qI(q)M(q)$  of choline-leucine



**Fig. 3** Total radial distribution function  $\text{Diff}(r)$  of choline-leucine

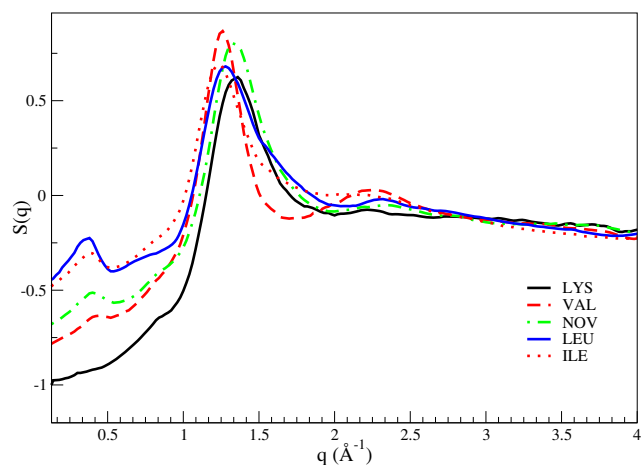


strongly dependent on the total number of electrons of the various systems. The  $S(q)$ 's for the five choline-amino acid ionic liquids considered in the  $0\text{--}4 \text{ \AA}^{-1}$  range (intermolecular interactions—pre-peak and main peak) are shown in Fig. 4.

Very interesting and diverse features can be pointed out from Fig. 4 analysis. First, if we consider choline-leucine and choline-isoleucine, two isomeric molecules that share the same maximal length of the side chain (3), we can notice that the pre-peak is present in both patterns and that it is found at  $0.38$  in leucine and at  $0.40 \text{ \AA}^{-1}$  in isoleucine, corresponding to correlation distances of  $16.53$  and  $15.71 \text{ \AA}$ , respectively. The positions of the main peak, instead, are inverted ( $1.24$  and  $1.28$ ). These observations could be tentatively explained, without a structural model, hypothesizing that the methyl group at  $\beta$  position increases the hydrophobic surface, resulting in stronger interactions. Concerning the valine-norvaline pair, it is evident that the arrangement of the three alkyl groups in the same chain, compared to branching, moves

the pre-peak position at lower  $q$  values of about  $0.04$  ( $0.44$  in valine,  $0.40$  in norvaline), while in the principal peak range, the opposite trend is observed ( $1.26$  valine,  $1.32$  norvaline), indicating that an additional group in the same chain increases its conformational degrees of freedom that can now fold more easily (more compact structure = lower distances = lower  $q$ ).

Yet, the most interesting aspect of  $S(q)$  analysis regards the total absence of a pre-peak in lysine diffraction pattern. Indeed, lysine has a longer alkyl chain than leucine (four terms, five if the terminal nitrogen is considered), and a pre-peak at even lower reciprocal distances would be expected. Actually, these results are in line with a series of diffractometric studies (see, for instance, Triolo et al. 2012) that pointed out that the nanosegregation of the apolar domains within the charged matrix is destroyed when a polar group is present in the chain. Consequently, the mesoscopic order that is signaled by the diffraction pre-peak disappears.

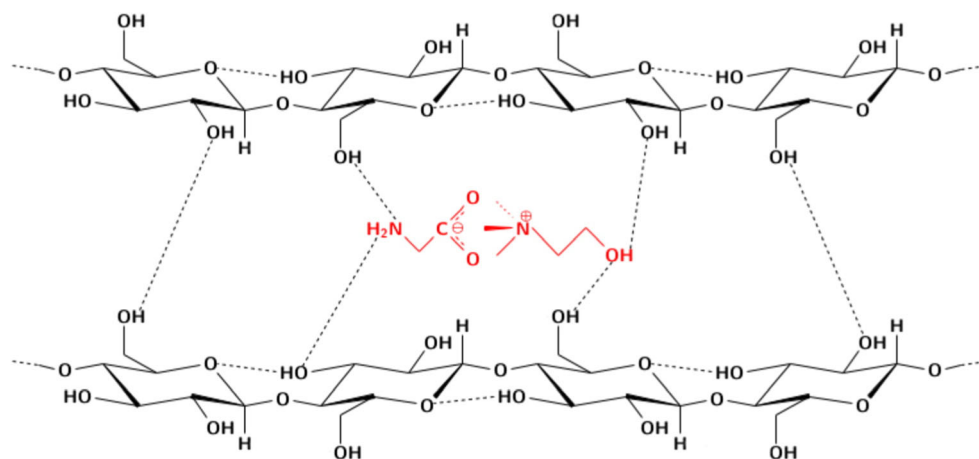


**Fig. 4** Atomic structure functions  $S(q)$  for Cho-Lys, Cho-Val, Cho-Nov, Cho-Leu, and Cho-Ile

## Recent applications

The complex and rich nature of the interactions occurring in ionic liquids that was described in detail in the previous paragraphs for ChoAA-ILs has already found a large number of applications in the field of biomolecules. Some detailed reports published in the last few years have described the strong affinity between ionic liquids and biomolecules, including peptides/proteins (Patel et al. 2014), DNA (Nakano et al. 2014), phospholipid bilayers (Benedetto et al. 2015), and saccharides (Paduszynski et al. 2013); the reader is referred to two complete reviews on the subject (Benedetto 2016a, 2016b) for additional references. Such a strong affinity, already observed for the more common ionic liquids, can be made even stronger when the ionic liquid itself shares a structural motif with the biomolecule, just as happens with

**Fig. 5** Putative mechanism of interaction between ChoGly and cellulose, adapted with permission from *J. Phys. Chem. C*, 2016, 120 (42), pp. 24088–24097. Copyright (2016) American Chemical Society



ChoAA-ILs. Indeed, their amino acid anions can be seen as preferential candidates to interact with peptides, and choline with phospholipid membranes. Two of the three new applications reported in the following paragraphs are based on interactions with biomolecules: polysaccharides in the first example and enzymes in the second one. The last example, instead, reports a potential use of ChoAA-ILs as proton conductors.

- Old paper preservation

One of the most striking applications is certainly in the domain of “Cultural Heritage” and regards the use of cholinium glycine to stabilize the cellulose structure, preserve its tensile strength, and prevent its oxidation (Scarpellini et al. 2016). Indeed, the study of mid-infrared spectra of artificially aged papers, non-treated and pre-treated with the IL, showed that the carbonyl peaks, that are used to quantify the degree of oxidation/acidification of cellulose, have lower intensity in IL-pretreated samples than those in non-treated ones. Probably, the Cho-Gly ion pair is able to intercalate within cellulose fibers by establishing hydrogen bond interactions between its  $\text{NH}_2$  and  $\text{COO}^-$  groups and hydroxyl groups of the polysaccharide (Fig. 5). The treatment with choline-ionic liquid could be seen, therefore, as a standard treatment for old paper preservation, with the large added value of non-toxicity for the operator.

- Biosensors

Another noticeable recent application of ChoAA-ILs regards the fabrication of screen-printed electrodes for enzymatic biosensors, in tandem with nanomaterials, such as multi-walled carbon nanotubes (CNT), graphene, or gold nanoparticles (Zappi et al. 2017). In this study, the liquids choline-glycine, serine, phenylalanine, and histidine were used as additives and were layered on the surface of the electrode before the enzyme adsorption. The strong IL-enzyme interactions assured its complete immobilization on the surface, with a resulting increase of the electrochemically active

areas; glucose oxidase, lipase, and alcohol dehydrogenase were tested. The best combination (largest active area) was obtained with a glassy carbon electrode with multi-walled carbon nanotubes and choline-phenylalanine. Probably, this very favorable behavior depends on the presence of the phenyl group in the amino acid that triggers a strong interaction between IL and carbon nanotube surface through stacking  $\pi$ - $\pi$  interactions (Woods et al. 2007); when other intermolecular interactions with the enzyme, among the many available for ChoAA-ILs, are added, an overall strong adhesion to the electrode results. These electrodes have been successfully applied to the analysis of various complex matrices, like olive oil samples, as well as to various beverages.

- Proton conduction

In a recent theoretical work (Campetella et al. 2017), the authors showed that whenever additional protic functions, like SH and COOH fragments, are present in the cation and anion side chains besides carboxylate in the anion and hydroxyl in cation, as it happens in cysteine and aspartic acid, an extensive migration of protons from these groups towards  $\text{NH}_2$  fragments takes place. These kinds of migration pathway, alternative to the highly hindered motion of the “big” choline and amino acid molecular ions, would be the only possible form of ionic conduction within a highly charged but very viscous medium, like ChoAA-ILs (Stoimenovski et al. 2010). This finding could hopefully pave the way for new electrochemical applications of these highly conductive non-aqueous media.

## Conclusions

The legion of ionic liquids has recently acquired very precious elements: choline-ionic liquids.

Prepared from renewable feedstocks, they are atoxic, endowed with highly solubilizing power, sometimes selective,

always really eco-friendly as a green-chemistry compound should be.

In this paper, a survey on the internal structure of these systems and how this is related to their properties has been given. Future developments of these compounds will probably explore their mixtures, the solutions with non-ionic liquids, and also the development of natural deep eutectic solvents, to further enhance their outstanding and sustainable properties.

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### Compliance with ethical standards

**Conflict of interest** Lorenzo Gontrani declares that he has no conflict of interest.

**Ethical approval** This article does not contain any studies with human participants or animals performed by any of the authors.

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