Isomerization patterns and Proton Transfer in ionic liquids constituents as probed by ab-initio computation.

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Abstract

We have recently shown that some protic ionic liquids (PILs) are characterized by an unexpected complex dynamic of proton transfer (M. Campetella et al., Phys. Chem. Chem. Phys. 19, 11869, (2017)). These liquids are based on a combination of cholinium cations and amino acid (AA) deprotonated anions. The side chain proton migration, can take place both within the same anion and between different anions. The intra-molecular proton transfer leads to a tautomerization of the AA anion that gives rise to the appearance of an anionic zwitterionic form. The inter-molecular proton transfer is chemically more interesting since it might, at least in principle, point to a way to achieve a dry, fast conduction in materials that are otherwise very viscous and typically poor conductors. We examine here, by means of ab-initio computations, the basic mechanism of proton transfer in a variety of AA anions to find promising candidates as new materials for electrochemistry applications.

1. Introduction

An ionic liquid (IL) is a pure electrolyte made entirely by ionic couples[1]. Because of their liquid state at room temperature and because of several advantageous properties, ILs represent a very active field of research due to a vast number of possible technological applications[2-5]. The implementation of biocompatible variants of these materials has opened new routes in the pharmacological and biomedical fields and, in general, in other green-chemistry processes[6-9]. In this respect, a new generation of ILs has been synthesized in which the typical inorganic anions such as $[PF_6]^-$, $[BF_4]^-$, Br^-, Cl^-, have been substituted by organic amino acid (AA) anions[10].

In this work we focus on the molecular components of ILs constituted by a choline cation $[Ch]^+$, and AA anions[11]. This class of ILs, given that their constituents play a role in metabolic processes, was proven to be non-toxic[12-14], and can be considered promising materials for bio-related applications[15-17].

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Given that, formally, these liquids come from an acid base reaction, they fall into the broad class of Protic ILs (PILs) [18-21]. Despite the simplicity of the composing molecular ions, this class of ILs shows very complex structural and dynamical features [22,23] due to the presence of H-bonds[24] whose strength obviously depends on the ionic partners and their relative acidity.

A PIL is generally synthetized using a simple acid-base reaction. The fate of the resulting materials and of its degree of ionization depends on the ΔpK_a between the acid and the conjugate acid of the base [25,26]. The larger the ΔpK_a, the more ionized the final material results [27]. In a completely ionized PIL charge transport is due to the motion of its bulky constituents and inversely proportional to the viscosity, thus leading to the well-known, poor conducting behavior of many ionic liquids. When the ΔpK_a is not large enough, the acid-base reaction is not quantitative and the ensuing liquid is a mixture of polar and ionic molecules. In this case, phase separation and evaporation of the polar component can occur, eventually nullifying the ionic liquid properties. It is therefore of great relevance for electrochemistry the discovery of conducting materials where the degree of ionization is still complete (so that they maintain the useful properties ascribed to ILs) but proton diffusion could occur [28-32].

In a recent work[33] we have shown that this might be indeed the case for two specific ionic liquids based on the cholinium cation $[Ch]^+$ and two AA anions that have an additional protic function on the side chain (–SH for $[Cys]^-$ and –COOH fors $[Asp]^-$). By carrying out ab-initio molecular dynamics, we have shown that in these liquids both inter- and intra-molecular proton transfer can occur. It is worth noting that AA anions have been previously shown to undergo proton transfer in imidazolium-based ionic liquids, although, in that case, the proton transfer took place between the cation and the anion producing a pair of neutral molecules. [34] The situation we are going to describe in the following is rather different because the proton transfer, in our case, does not neutralize the ionic pair and the liquid remains ionized.

Intra-molecular proton transfer gives rise to a peculiar tautomer of the AA anion which is a zwitterion moiety, but where the charge separation now takes place in the anion. Formally this molecular anion has a triple charge separation that, to be stabilized, requires the presence of a medium with a relatively high dielectric constant. Conformational studies of typical AAs (and of their protonated and deprotonated forms) have been undertaken exhaustively in the literature and the relative stability of the various tautomers have been systematically analyzed often in comparison with spectral data (see for example refs. [35-37]). In particular, computational evidence for the existence of the anionic-zwitterionic tautomer for $[Glu]^-$ has been provided by Turan and Selçuki[38] and Floris et al. [39]. Computations on the anionic-zwitterionic form are also available for $[Cys]^-$, where it has been found as a possible stable anionic form in a model solvent.[40] In many

other theoretical studies, however, the possibility of forming an anionic zwitterion has been overlooked [41,42], probably because such structure, to converge, needs a dielectric medium and most computations have been carried out in vacuo. The presence of unconventional zwitterionic tautomers has been recently demonstrated experimentally for [Cys] that, under certain conditions, exists as a zwitterionic structure with a thiolate group. [43]

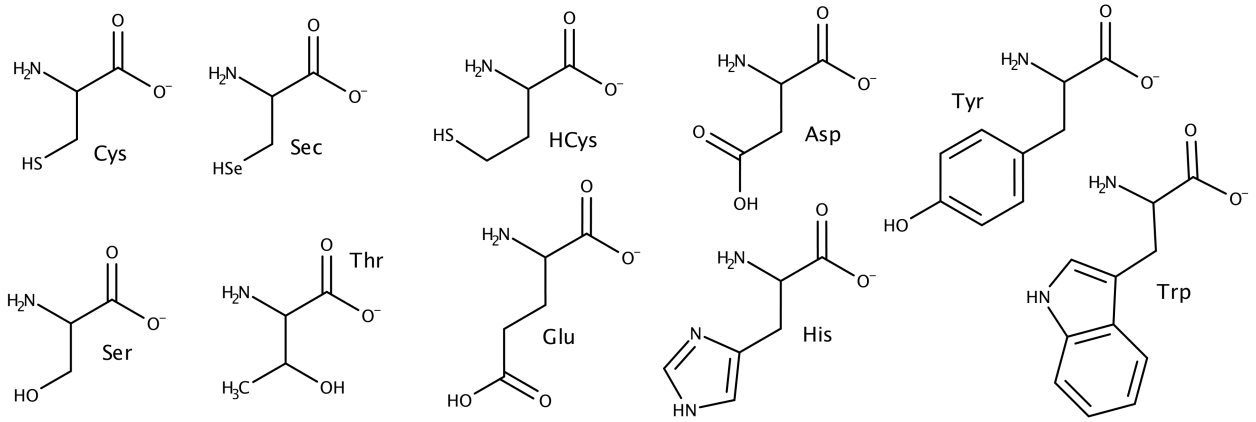
Inter-molecular proton transfer in amino-acid based protic ionic liquids is a more elusive process and has not been characterized before in these specific compounds. For the proton transfer to occur, two anions with the right acid-base pair must come close enough in the liquid to support the proton migration. This may be difficult because in a typical ionic liquid each anion is surrounded by cations and vice versa. We have found computational evidence [33] of inter-molecular proton transfer in [Asp][Ch] and, to a lesser extent, in [Cys][Ch]. In the former, the proton transfer was a frequent event on the timescale of the simulations (~50 ps) and turned out to be possible because of the favorable geometry of the bulky $[Asp]^-$ anions whereby their relatively large molecular size allowed them to come into close contact with each other through H-bonds. The electrostatic repulsion between the two anions was then minimized probably by the fact that the two, negatively charged, carboxylates were separated by a sufficiently large distance.

In this work, we expand the set of possible AA candidates by computing, through high quality ab-initio methods, the energy profiles for both inter- and intra-molecular proton transfer. We have limited our calculations only to those AAs that, even though in anionic form, still have a second protic function on the side chain.

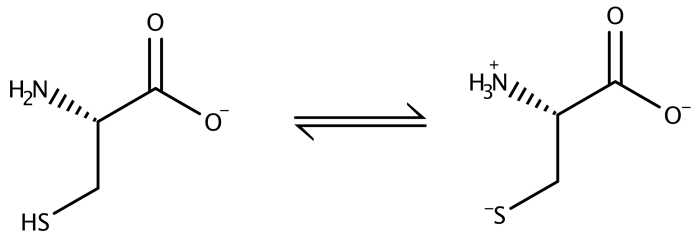
2. Methods

The chemical systems which are the target of this study are composed by a choline cation and the 10 AA anions reported in Scheme 1 (serine [Ser], threonine [Thr], cysteine [Cys], homocysteine [Hcys], seleno-cysteine [Sec], aspartic acid [Asp], glutamic acid [Glu], histidine [His], tryptophan [Trp], and tyrosine [Tyr]). We have explored both intra- and inter-molecular proton transfer, i.e. we have performed the computations either on the isolated anion or on a pair of anions. The reactions for intra and inter-molecular proton transfer are reported in Scheme 2 and in Scheme 3 respectively using [Cys] and [Asp] as examples. Since the first carboxylic proton has been removed to generate the AA anion, we are taking into consideration only the transfer of the additional proton on the side chain. In addition, we have limited our exploration to those conformers where the side chain proton points either toward the amino group of the same molecular ion or to the amino group of another adjacent anion. It therefore follows that we did not attempt a full conformational space exploration since we are interested only to those structures that present a geometry that can promote a proton transfer. When possible, we have located the transition states for the proton transfer reaction.

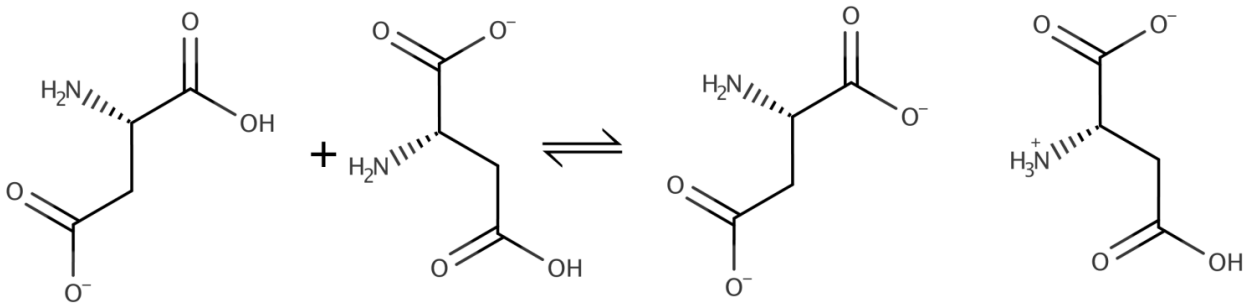
The calculations have been performed both in gas-phase and in a continuum solvent model (PCM). Since the dielectric permittivity of these compounds has not been reported in the literature so far, acetonitrile has been employed as a model solvent given that its dielectric constant has the typical value of protic ionic liquids [44] (for further information on the use of the PCM model, see the supporting information, Section S1 and Figure S1).



Scheme 1: chemical structures of the 10 AA anions examined in this work.



Scheme 2: Intra-molecular proton transfer. Left: anionic form, right: zwitterionic-anion form.



Scheme 3: Inter-molecular proton transfer. The reaction can be rationalized as $A^- + A^- \rightarrow A^{2-} + A$

The characterization of the intra-molecular proton transfer reaction (Scheme 2) has been initially performed at the B3LYP/6-311+G** and MP2/6-31+G** levels for all AAs anions reported in Scheme 1. Optimized geometries of the anionic, zwitterionic-anionic and transition state structures (when possible) have been obtained with both methods and characterized by evaluating harmonic frequencies. By looking at the transition state normal modes we have ensured that the one relative to the negative hessian eigenvalue was dominated by the proton motion and that we had located the correct transition state.

Atomic partial charges and electronic population of each critical point have been analyzed using atomic polar tensors (APT) [45] and natural bond orbital (NBO) [46] analysis.

The above computations have allowed us to select a subset of 5 AA anions ([Cys], [Hcys], [Sec], [Glu] and [Asp]) obtained by excluding those for which the energy of the anionic-zwitterion was much larger than the anion and therefore tautomerization was very unlikely to occur to any extent. For the subset of 5 AA anions we have repeated the geometric optimizations at the MP2/6-311+G** level for a more reliable assessment of the final energies.

The computation of the intra-molecular proton transfer profile (see Scheme 3) has been performed only for these five AA pairs and only at the B3LYP/6-311+G**/PCM level.

The $[Cys]^-$ and $[Asp]^-$ AA anions have been used in a series of calculation to test the accuracy of the methods. For these systems, a series of functionals, namely M062X[47], PBE0[48], BLYP[49,50], BMK[51], CAM-B3LYP[52] and PBE[53] have been used. The relative energies and final geometries obtained by different functionals agree well with each other with few exceptions. The effects of empirical dispersion corrections, obtained by repeating the computation using D3-B3LYP[54] and ωB97XD[55], have also been evaluated and found to be small. More details, as well as energies and geometric differences can be found in the supporting information in Section S2. The Gaussian09[56] package has been used for all calculations.

3. Results and discussion

3.1 Intra-molecular proton transfer

A sketch for the intramolecular proton transfer is reported in Scheme 2 where we use the $[Cys]^-$ AA as an example. The movement of the proton from the side chain to the amino group brings an additional charge separation to the molecular ion creating an anionic-zwitterionic tautomer[38-40]. In the rest of this work we will refer to the structure with a high charge separation as zwitterionic although it must be kept in mind that these structures do not corresponds to the typical neutral zwitterionic forms of AAs that can be found in solution, that are isomers of neutral molecules. The isomerization pattern that we have depicted in Scheme 2 has an important role not only from the

point of view of the proton mobility, but it may substantially alter the nanoscopic structure of the fluid and, in turn, determine the bulk properties. Determining the likelihood of the existence of such forms for AA anions by energy consideration is therefore crucial to understand the bulk behavior of the ionic liquids whose anionic molecular component is a deprotonated amino-acid [10-14].

To explore the peculiar electronic density of the zwitterionic tautomers, the partial atomic charges have been evaluated using the APT and NBO analysis for some of the representative AA anions tautomers using both the MP2 and B3LYP electronic densities. In Table S5 (supporting information) we report, as an example, the partial atomic charges for [Cys] and [Hcys]. First, we note that MP2 and B3LYP give essentially the same results. APT and NBO charges are qualitatively in agreement (i.e. they provide the same polarity) even though the charge values are different as expected [57]. In the anionic isomer, the negative charge is obviously localized on the carboxylate oxygen group, the –SH group is approximately neutral and the $–NH_2$ bears a small negative charge. In the zwitterionic isomer the $–NH^+_3$ group is positively charged with values around +0.6 (NBO) and the sulfide group has a negative charge of -0.7 (NBO). The carboxylate remains similarly negatively charged in both isomers. The charge distribution in the transition state is intermediate between those of the two isomers.

The optimal geometries of the anionic, zwitterionic and (when possible) transition state (TS) structures have been evaluated for the 10 AAs reported in Scheme 1. The resulting relative electronic energies in kcal/mol for B3LYP and MP2 are reported in Table 1. We have used the anionic energy (E_{AA}) as reference for both the zwitterionic form (E_{ZW}) and for the transition state (E_{TS}).

We begin by analyzing the B3LYP results. First, it is possible to note that for 4 AA ([Ser]-$^-$, $[Thr]^-$, $[Asp]^-$ and $[Glu]^-$) the anionic-zwitterionic structure is simply unstable in vacuo (the structures are indicated by an “u” in the table). This happens when the proton is on an oxygen atom of the side chain, like in $[Ser]^-$ and $[Thr]^-$ (with hydroxyl group on side chain) or in both $[Asp]^-$ and $[Glu]^-$ (with a carboxyl group). An exception is represented by $[Tyr]^-$ where the phenolic group, given its well-known acidity, provides an additional stability to the separate charge specie.

*Table 1. B3LYP/6-311+G** and MP2/6-311+G** energy differences of the zwitterionic and TS structures with respect to the anionic one in vacuo and in PCM in kcal/mol. Unstable structures are identified with "u". The absence/impossibility of a transition state is indicated with "f".*

AA^-	B3LYP				MP2			
	Vacuo		PCM (ε=35.7)		Vacuo		PCM(ε=35.7)	
	E_{ZW}	E_{TS}	E_{ZW}	E_{TS}	E_{ZW}	E_{TS}	E_{ZW}	E_{TS}
Ser	u	-	28.3	f				
Thr	u	-	29.0	f				
Cys	5.7	7.6	**-0.4**	6.2	8.0	8.6	**2.5**	7.5
Hcys	1.0	2.7	**-2.3**	2.7	2.5	3.4	**-0.1**	3.7
Sec	-1.0	4.7	**-6.2**	4.6	-1.7	4.2	**-6.8**	4.5
Asp	u	-	**-0.3**	1.2	u	-	**0.9**	1.8
Glu	u	-	**-0.1**	1.4	u	-	**0.0**	0.7
His	17.1	17.1	8.6	10.4				
Trp	10.4	f	15.4	f				
Tyr	9.4	f	7.3	f				

By introducing a "solvent" through PCM (ε=35.7) all zwitterionic structures become stable. Table 1 shows that the relative energy content of the anionic-zwitterionic forms of $[Ser]^-$, $[Trp]^-$ and $[Thr]^-$ are much larger (up to more than 20 kcal/mol) than their anionic counterpart and we conclude that isomerization for these AAs is highly improbable. This result is somewhat expected by considering the pK_a of the proton donor group: ~17 for alcohols and 16 for indole. The anionic zwitterions of $[Tyr]^-$ and $[His]^-$ appear at a lower energy (between 7 and 8 kcal/mol that is consistent with their lower pK_a values, ~10 for phenol and ~14 for imidazole), but nevertheless the energy of the anionic-zwitterionic form is still high enough to prevent its existence in the ionic liquid environment. The energy difference E_{ZW} for the rest of the AAs (bold typeface in Table 1) are instead small and negative, i.e. for these AAs the anionic-zwitterionic isomers are more stable than the anionic counterparts at least in an average dielectric medium. It is worth noting that for $[Sec]^-$ the anionic zwitterionic form turns out to be the most stable isomer even in vacuo.

In Table 1 we also report (where possible) the relative energies of the transition states (E_{TS}) to evaluate the energy barrier to intra-molecular proton transfer. In $[Trp]^-$ and $[Tyr]^-$ the determination of E_{TS} is impossible because the conformation of the molecule does not permit to have a simple (one step) mechanism for the proton transfer between the protic chain and the amino group. In addition, it has not been possible to determine the TS structures for $[Ser]^-$ and $[Thr]^-$ because of a

flat potential energy surface between the two minima. To try to locate the TS for these two AAs, we performed a relaxed potential energy surface scan along the donor-proton distance. The potential profile shows a monotonic behavior going from the zwitterionic form (at higher energies) to the anionic one. Their potential energy surfaces are reported in the supporting information in Figure S2.

$[Cys]^-$, $[HCys]^-$ and $[Sec]^-$ show relatively small barriers to proton transfer (4.7-7.6 kcal/mol) that may allow the isomerization process to equilibrate fairly rapidly at room temperature. Among the most interesting results, the $[Asp]^-$ and $[Glu]^-$ cases present a very low energy barrier thereby indicating that the proton dynamics and the ensuing isomerization processes in these molecules can be easily activated even at low temperatures.

As we have mentioned before, all the AA structures have been also optimized using MP2/6-31+G**. The resulting energies are reported for completeness in the supporting information in Section S4, Table S3. For the subset of 5 AA anions where both E_{ZW} and E_{TS} were found to be sufficiently low, we have repeated the MP2 computations using a triple zeta basis set and we report the results in Table 1. The MP2 results agree well with B3LYP in vacuo where, for example, both methods predict a gas-phase, stable [Sec] anionic-zwitterion isomer which is further stabilized (6-7 kcal/mol) with respect to the anionic form when in a dielectric. As for B3LYP, MP2 predicts the anionic-zwitterionic forms of $[Asp]^-$ and $[Glu]^-$ to be almost isoenergetic with their respective anions and the barrier to proton transfer for both to be very small. The $[Cys]^-$ and $[Hcys]^-$ anions, instead, represent a peculiar case where MP2 and B3LYP disagree substantially in positioning the relative energies of the two isomers, although they agree to a certain extent in the evaluation of the barrier height. The reason for disagreement can be attributed to the way in which PCM is implemented in MP2 computations and to the fact that the solvent perturbation is evaluated on the reference only. Given that all the high accuracy hybrid functionals that we have tested on the [Cys] AA (see Table S1) predict the E_{ZW} value to be negative, we conclude that the B3LYP results appears here to be more robust than the MP2 one.

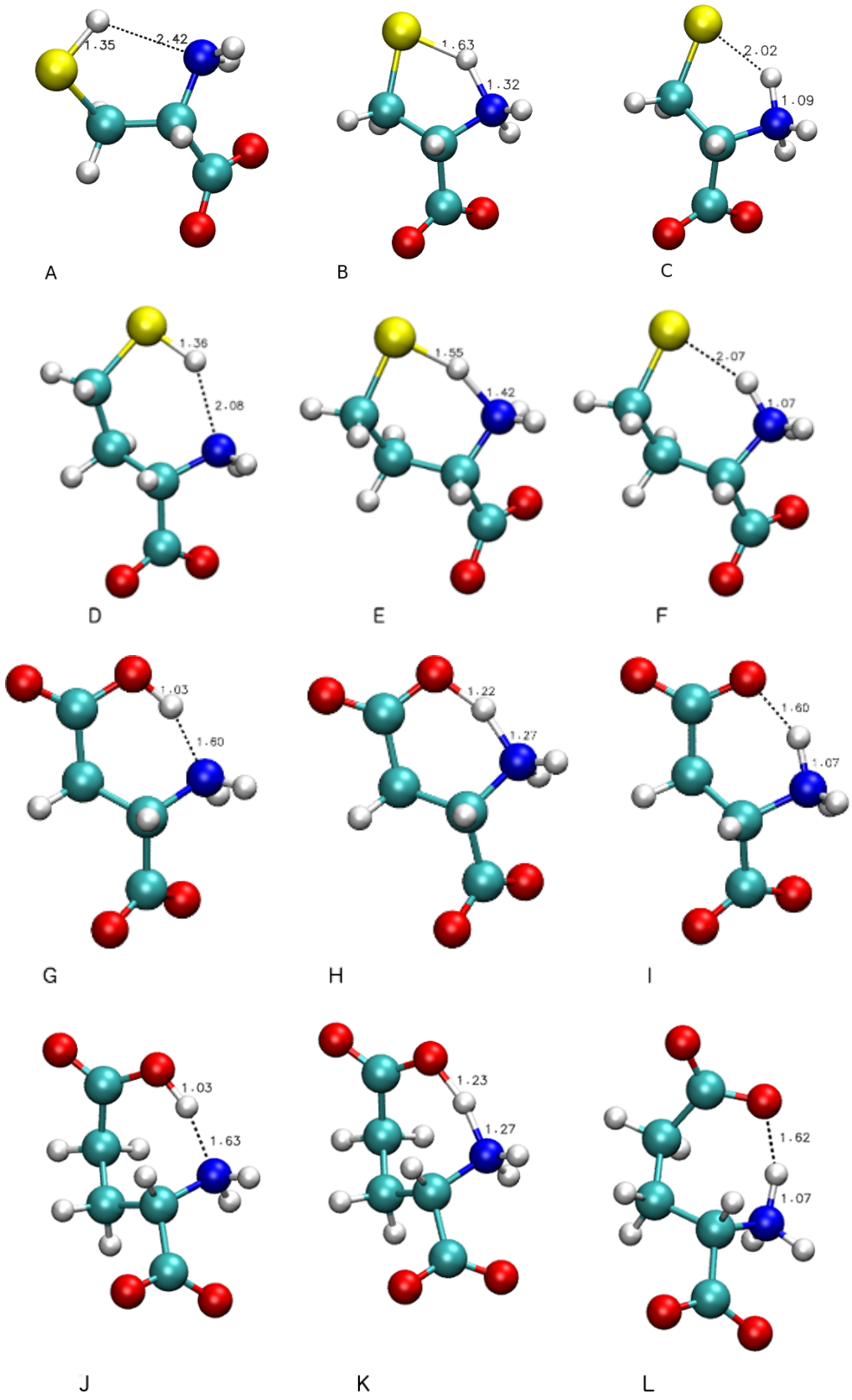


Figure 1: Example of anionic (left), zwitterionic (right) and TS structures (center) of $[Cys]^-$ (A,B,C), $[HCys]^-$ (D,E,F), $[Asp]^-$ (G, H, I) and $[Glu]^-$ (J, K, L).

We present in Figure 1 the structures of the $[Cys]^-$, $[HCys]^-$, $[Asp]^-$, $[Glu]^-$ AA anions as obtained from the B3LYP calculations (the case of $[Sec]^-$ is not illustrated in the figure, but it resembles the $[Cys]^-$ one). As mentioned above and as shown in Table S2, the changes in geometry between B3LYP and MP2 were found to be small and therefore we decided to show only the B3LYP structures here.

To further elucidate the geometry, in Table 2, we report the donor-H (D-H) and acceptor-H (N-H) distances before (AA), after (ZW) and during isomerization (TS). In the anionic structures, the minimum geometry has the H atom on the side chain oriented toward the N atom (see Figure 1). A D—H···N hydrogen bond is established. For an S atom on the side chain ($[Cys]^-$ and $[HCys]^-$) the S-H distance is 1.35-1.36 Å; while with the Se atom ($[Sec]^-$) the distance increases to 1.5 Å; finally, with the carboxyl group, the D-H distance is about 1.0 Å. The distances between the proton and the acceptor N in the anionic form, depends on the flexibility of the molecular structure and on size of the ring structure induced by the presence of the H-bond. For a 5-member ring ($[Cys]^-$ and $[Sec]^-$, see for example molecule A in Figure 1) the distance is quite large (about 2.5 Å) , but it is reduced for a 6-member ring ($[HCys]^-$ or $[Asp]^-$, see molecule D and G in Figure 1) or a 7-member ring for $[Glu]^-$ (molecule J in Figure 1). The N—H distances of the zwitterionic structures are all very similar and around 1.1 Å, a typical value for the H—N^+ bond in ammonium compounds. Obviously, the bond lengths of TS are intermediate between the values of anionic and zwitterionic structures.

*Table 2: B3LYP/6-311+G** PCM (ε=35.7) Selected bond lengths in the anionic (left), zwitterionic (center) and TS structures (right) in Angstroms.*

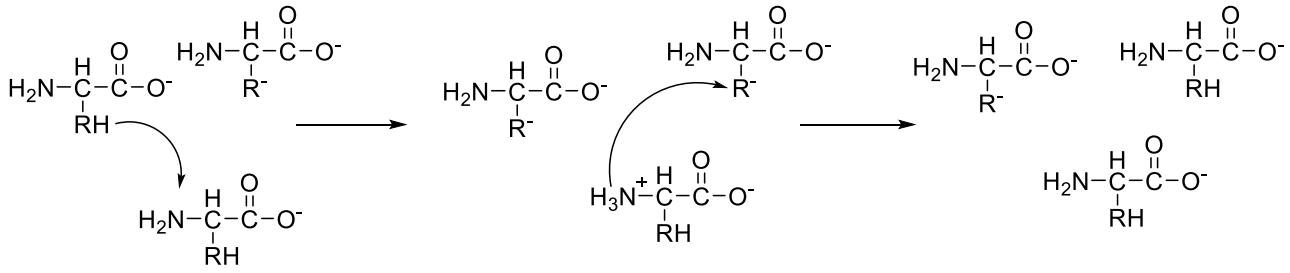
	AA		ZW		TS	
AA^-	d(D-H)	d(H-N)	d(D-H)	d(H-N)	d(D-H)	d(H-N)
Cys	1.35	2.53	2.23	1.05	1.57	1.41
Cys[a]	1.34	2.44	2.16	1.05	1.57	1.36
HCys	1.36	2.08	2.08	1.07	1.55	1.42
HCys[b]	1.34	2.13	2.00	1.07	1.55	1.37
Sec	1.47	2.67	2.37	1.05	1.63	1.52
Asp	1.03	1.60	1.60	1.07	1.22	1.27
Glu	1.03	1.63	1.62	1.07	1.23	1.27

[a, b] *MP2/6-311+G** PCM (ε=35.7) data*

3.2 Inter-molecular proton transfer results

The process on inter-molecular proton transfer can be modeled by coupling two anions so that their negatively charged carboxylate terminals are far away from each other. The inter-molecular proton transfer is reported in Scheme 3 for $[Asp]^-$ where we can see that the displacement of a proton from the carboxylic acid to the amino group of the nearby anion give rise to a di-anion and to a neutral zwitterion. This kind of proton transfer is not uncommon in AAs since is at the basis of the so called "salt bridge" formation in heterogeneous AAs pair such as Asp/Glu···Lys/Arg[58]. It is our opinion that this reaction might represent the crucial elementary step which is part of the proton transfer chain in the liquid. A possible reactive path for proton transfer is reported in Scheme 4 where we can see that the proton drift through the liquid takes place via a mechanism that involves more than two molecules, but nevertheless can be thought of being made by the repetition of the same elementary step reported in Scheme 3 or by its inverse. This is not pure speculation as we have already seen such complex concerted mechanisms to take place in the simulations reported in ref. [33].

The study of the reaction in Scheme 3 therefore represent the main reactive event in the proton migration chain and its study is important because such process can be considered as the rate determining step in the whole process.



Scheme 4: Possible proton transfer migration reaction in bulk liquid.

We have optimized the geometries for several pairs of AA anions, but we have limited the exploration only to those we proved before having a small barrier for the intra-molecular proton transfer. The relative energies at the B3LYP level for the inter-molecular proton transfer are reported in Table 3 where the energy of the reactants (left of Scheme 3) is taken as reference. The formation of the "salt bridge" is exo-energetic for all the AAs examined here and the proton transfer barrier energies are very low. One of the most interesting case is $[Glu]^-$ where the A^-+A^- and the $A^{2-}+A$ isomers are almost iso-energetic and where the single-step mechanisms of Scheme 3 can therefore be easily reverted to yield the proton migration of Scheme 4.

2AA	$E(A^- + A^-)$	$E(A^{2-} + A)$	E_{TS}
Cys	0	-4.0	3.5
Hcys	0	-4.6	1.1
Sec	0	-4.8	1.6
Asp	0	-4.2	1.4
Glu	0	-0.2	1.0

*Table 3: B3LYP/6-311+G** PCM (ε=35.7) energy differences for intermolecular proton transfer in kcal/mol.*

The corresponding minimum energy structures for $[HCys]^-$ and $[Asp]^-$ are reported in Figure 2 as examples of the 5 systems explored. The situation for $[Cys]^-$ and $[Sec]^-$ are very similar the one reported for $[HCys]^-$, and the one for $[Glu]^-$ resembles the one reported for $[Asp]^-$.

In the $[Asp]^-$ system, the proton transfer takes place via a minimal rearrangement of the geometric configuration. In particular, the only noticeable change between the complex on the left and that on the right is the rotation of the COOH group with the formation of an intermolecular COOH···OOC H-bond. In the $[HCys]^-$ system, instead, we have a substantial geometric difference between the $A^- + A^-$ channel and the transition state thereby indicating that a substantial geometric rearrangement must take place to allow the proton transfer. Initially, both the $[HCys]^-$ anions present an intra-molecular H-bond binding the S—H to the amino groups. In the present case, during the reactive process of Figure 2, both H-bonds must be broken to bring the reactants (left) to the TS (center). One H-bond is then reformed in the product state (right).

3.3 Quantum corrections

When the reaction barriers are low as in many of the above examples the quantum corrections due to zero-point-energies (ZPE) can be extremely important. Obviously, when adding the (positive) contribution of the ZPEs, the absolute energy of the reaction profiles is globally increased. There are however peculiarities in the vibrational patterns of the reactants and products that can alter significantly the energy differences and hence the thermodynamics. In addition, the relative energy of the transition state is lowered by the fact that a saddle has one normal mode less than the minima and its ZPE content is smaller. We should note that the computation of quantum ZPE effects is performed in the harmonic approximation and that the results slightly overestimate the real anharmonic ZPE. The widely accepted ZPE scaling factor for B3LYP is between 0.96 and 0.98 which is a value that does not alter significantly our results.

We report in Table 4 the ZPE corrected B3LYP relative energies for a selected subset of AA for the same reactive processes described by Scheme 2 (intramolecular proton transfer) and Scheme 3

(intermolecular proton transfer). For completeness, we have also reported the Gibbs free energy values. We point out that the free energy values are computed according to the perfect gas approximation and therefore their reliability in describing the molecules in the liquid is questionable. An analogous set of data has been obtained using MP2/6-311+G**, but since they show the same trend, they have been reported in Table S4 in the supporting information.

Accounting for quantum effects has important consequences on both the thermodynamics and the kinetic of the reactive processes of Scheme 2 and Scheme 3. We see that for the intra-molecular proton transfer (upper half of Table 4) the isomerization reaction becomes endo-thermic (and endo-energetic in terms of free energies) except for $[Sec]^-$ and that the barrier to proton transfer are lowered significantly and even disappear for $[Glu]^-$ and $[Asp]^-$ (compare with Table 1).

In the case of the inter-molecular proton transfer the reaction tend to remain exo-thermic (except for $[Glu]^-$) but the gain in energy is clearly diminished by quantum effects. Also in the inter-molecular case, we see that the inclusion of ZPE substantially lowers the kinetic barrier to proton transfer (compare with Table 3).

AA^-	E_{AA}	E_{ZW}	E_{TS}	G_{AA}	G_{ZW}	G_{TS}
Cys	0	2.8	5.5	0	3.7	6.6
HCys	0	0.3	1.5	0	0.8	2.0
Sec	0	-2.3	4.1	0	-1.5	5.1
Asp	0	0.2	-0.7	0	0.3	-0.4
Glu	0	0.4	-0.7	0	0.03	-0.9
$2AA^-$	$E(A^- + A^-)$	$E\ (A^{2-} + A)$	E_{TS}	$G(A^- + A^-)$	$G\ (A^{2-} + A)$	G_{TS}
Cys	0	-1.3	2.5	0	1.3	4.9
HCys	0	-1.0	0.4	0	3.3	3.9
Sec	0	-1.4	1.0	0	-0.8	2.8
Asp	0	-3.1	-0.4	0	-2.1	-0.3
Glu	0	0.4	-1.0	0	0.6	-0.3

*Table 4: B3LYP/6-311+G** PCM (ε=35.7) ZPE-corrected relative electronic energies and relative free energies. See text for details.*

The differences in terms of Gibbs free energies substantially follow the enthalpic ones, except for [Cys] and [HCys] where the ΔE and ΔG have different sign.

The results reported in Table 4 look very promising from the point of view of the mechanism depicted in Scheme 4 because they tell us that the enthalpic difference between the reactants and the

products in an inter-molecular proton transfer is reduced when quantum effects are accounted for (compare the E_{ZW} values reported in Table 3 and in Table 4). Therefore, the proton transfer reaction appears to be reversible and reversibility is a key factor for the occurrence of the proton migration mechanism reported in Scheme 4. In addition, it appears that quantum effects lowers significantly the proton transfer kinetic barrier for all the aminoacids therefore making the proton transfer process fast at room temperature. In conclusion, our calculated data show that, very likely, the intra-molecular proton transfer process is reversible and hindered by a low kinetic barrier or no barrier at all for several AA anions. This is a crucial conclusion in the view of the possibility of the instauration of a proton migration mechanism that might resemble the Grotthuss one in water.

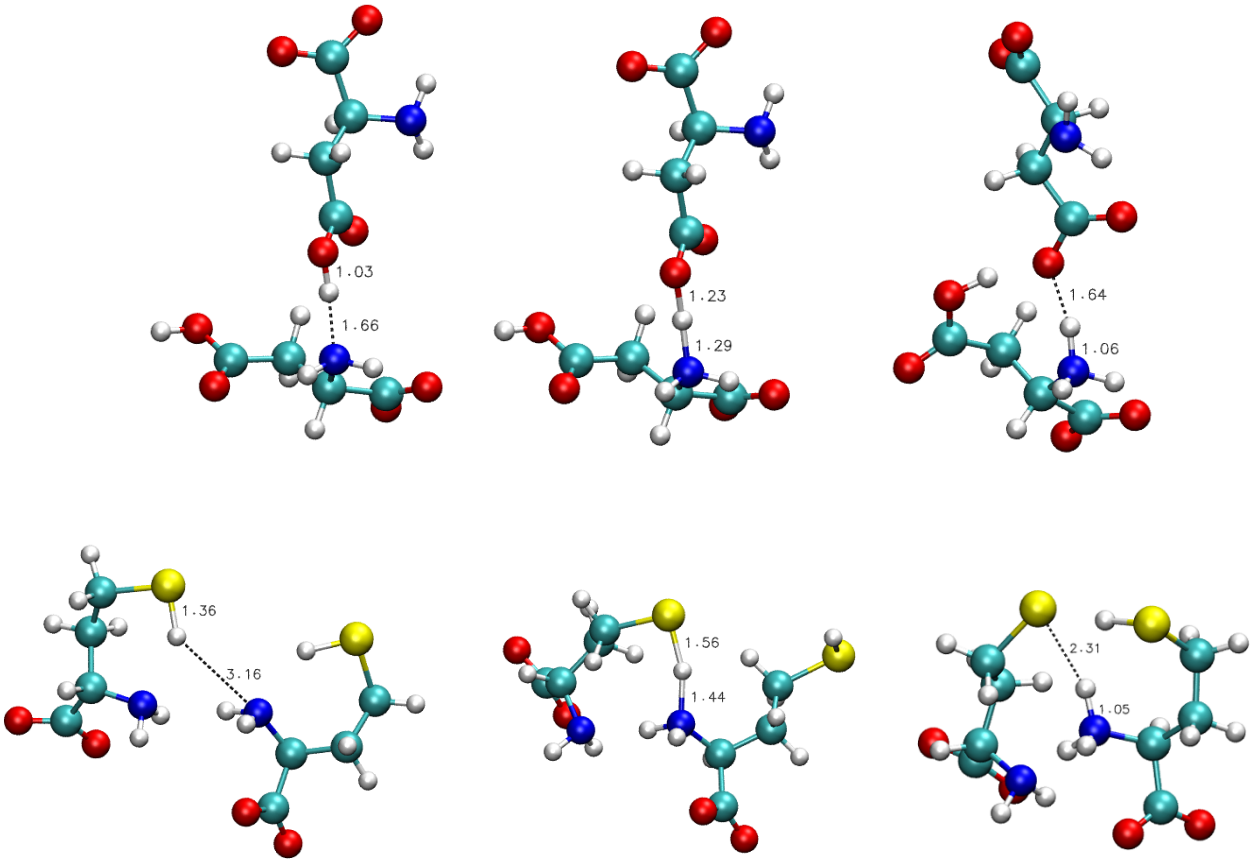


Figure 2: Optimized structures (from left to right, reactants, TS and products) for the intermolecular proton transfer: above $[Asp]^-$, below $[HCys]^-$.

4. Conclusions

We have reported a series of calculations on possible isomerization paths in the molecular constituents of ionic liquids containing AA anions. While the isomeric and conformational freedom of AAs is well known, we focused here exclusively on the isomerization reactions that can take

place at the expenses of the deprotonated variant of AAs since they represent the anionic constituents of a class of interesting ionic liquids. In these liquids, the AAs have lost their most acidic proton and neutralization reactions can occur only to a limited extent because the entire liquid must maintain its global electrical neutrality. In addition, we should emphasize that the dielectric environment in an ionic liquid is rather different from water and that specific pK_a measurements are not available. Therefore, the expected order of basicity of the various substituents and of the aminoacid side chain can be substantially altered in the ionic liquid environment.

We have proved, using ab-initio calculations, that the isomerization paths are energetically accessible for a variety of aminoacids provided they are surrounded by a dielectric with a sufficiently high constant to stabilize the charge-separated species. The possibility of having both inter and intra molecular proton transfer has been explored.

We have found that, in a dielectric with a constant like that of protic ionic liquids, isomerization reactions which involve the side chain proton can effectively occur both thermodynamically and kinetically. The most interesting cases are represented by the sulfur containing AAs as $[Cys]^-$ and $[HCys]^-$ and by those AA that have a second carboxylic terminal on the side chain, $[Glu]^-$ and $[Asp]^-$. It is very likely that in the bulk liquid the normal deprotonated form of the AA is in equilibrium with an anionic zwitterion isomer and that this fact could have a strong influence on the bulk properties of the liquid.

We have also found that proton transfer can take place between two different anions and that the reaction, in this case, brings the two anions into a neutral zwitterion and a di-anion. This mechanism seems to be exothermic for most AA anions and particularly favorable for [Asp] and $[Glu]^-$ AAs where the barrier to proton transfer has been found to be very small.

A small energy barriers together with reversibility (i.e. a similar energy of product and reactants) are the necessary conditions for the proton transfer process to “propagate” in the liquid. In this respect, we have proven by calculation, that the intermolecular proton transfer reaction is indeed reversible for several AAs leading to the conclusion that the resulting ionic liquids can be a viable prototype chemical systems in which a dry proton conduction can take place. In particular, we have provided evidence that it might be possible to obtain fast charge transport in dry ILs by using a tunable molecular structure with the right protic groups.

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Supporting Information

S1: The choice of the dielectric constant. S2: DFT/functional performance on [Cys] and [Asp]. S3: [Ser] and [Thr] potential energy surfaces. S4: MP2 energies. S5: APT and NBO charges.

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