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ORIGINAL ARTICLE

Ion-selective interactions of biologically relevant inorganic ions with alanine zwitterion: a 3D-RISM study

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Abstract The ion-molecular association between inorganic ions and the charged groups of alanine zwitterion in biologically relevant aqueous salt solutions, namely NaCl(aq), KCl(aq), $MgCl_2$(aq), and $CaCl_2$(aq), has been investigated over a wide range of electrolyte concentration. The influence of salt concentration on the stability of the formed ion-molecular associates is analyzed. The structure of the formed aggregates and its dependence on salt concentration and chemical nature of the inorganic ion are discussed.

Keywords Amino acid · Aqueous electrolyte solution · Ion-binding · 3D-RISM integral equation method

Introduction

Amino acids, both as free molecules as well as constituents of proteins, were and are objects of considerable attention because of their important role in different biological processes in living organisms. It is well known that the environment where biomolecules act is defined by the presence of water molecules and inorganic ions. Salt addition to this environment generally produces considerable changes in many biomolecular properties (Brooks and Nilsson 1993; Carta and Tola 1996; Kohn et al. 1997; Kumar 2001; Hamelink et al. 2002; Dixit et al. 2002; Lee et al. 2002; Auffinger and Hashem 2007). In particular, changes in protein solubility, hydration, denaturation and aggregation behavior, etc. depend on the nature of the salts (von Hippel and Schleich 1969; Cacace et al. 1997). Moreover, already by their charge inorganic ions have a large unspecific effect as biological processes, ranging from signal transduction via the control of reaction specificity to macromolecular structure, depend on electrostatic interactions among the polar and ionic species ubiquitous in intra- and extracellular fluids (Stryer 1988). The investigation and modeling of entire biomolecules in water–salt media is often inconvenient because of difficulties with separating the various effects originating from the many types of interactions prevailing in such systems (Maréchal 2007). For this reason, amino acids having isolated functional groups typical for biomolecules are conveniently used as model compounds to investigate ion-selective interactions of inorganic ions with protein surfaces. Some progress has been made in understanding the effects of simple ions (Kunz et al. 2004; Collins and Washabaugh 1985), but a clear understanding of their molecular origins in complex biological systems has been more elusive.

In this paper we present the results of a statistical mechanics study of ion-molecular association of alanine (Ala) in biologically relevant electrolyte solutions, namely NaCl(aq), KCl(aq), $MgCl_2$(aq), and $CaCl_2$(aq). L-Alanine is the smallest natural amino acid that is chiral. It is a constituent of nearly all natural peptides and natural polypeptides. Alanine is an important energy source for muscles, brain, and central nervous system; it strengthens the immune system by producing antibodies and actively participates in metabolism of sugars and organic acids (Perutz 1992). It should be noted that in the aqueous phase at neutral pH, amino acids exist as zwitterions (ZW) bearing simultaneously charged ammonium and carboxylate moieties. Figure 1 shows the alanine zwitterion (Ala-ZW) molecule,

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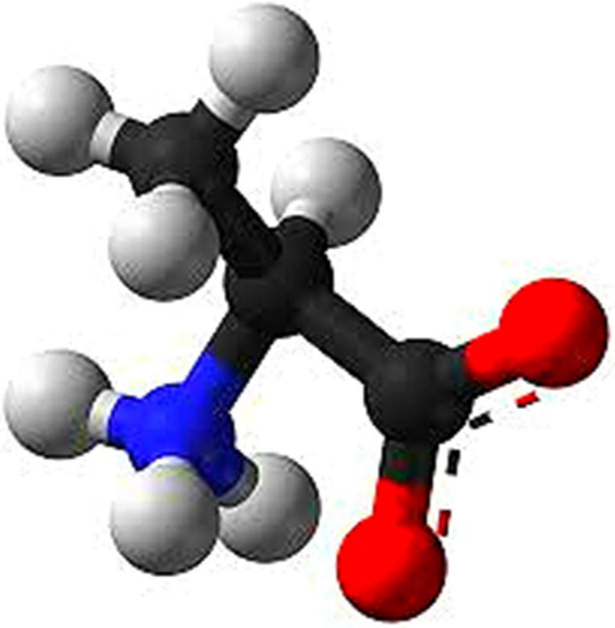

Fig. 1 Spatial configuration of Ala-ZW

$NH_3^+CHCH_3COO^-$, consisting of the charged hydrophilic $-COO^-$ and $-NH_3^+$ groups and the hydrophobic moiety formed by the methyl group, $-CH_3$, and the CH fragment. As it can been seen from Fig. 1, Ala-ZW is an asymmetric molecule where symmetric groups are linked via the chiral center.

The last decades saw a significant growth in the number of studies for zwitterionic amino acids in biologically relevant aqueous electrolyte solutions. However, with regard to Ala-ZW, there are only few papers devoted to its hydration structure in water (Kameda et al. 2003; Degtyarenko et al. 2007, 2008; Fukuyama et al. 2005; Fedotova and Dmitrieva 2013) and no studies on the problem of possible ion-binding to this amino acid. The aim of this paper is to study the features of ion-molecular association between monovalent and divalent inorganic ions and the charged functional groups of Ala-ZW and to elucidate the dependence of this aggregation process on salt concentration. To this end, we used integral equation theory in the 3D-RISM (three-Dimensional Reference Interaction Site Model) approach to calculate the spatial (3D-) density distribution of solvent atoms (sites) in a local coordinate system linked to the solute molecule.

Method and computational details

The 3D-RISM theory was described in detail elsewhere (Kovalenko 2003) including our recent papers (Fedotova and Kruchinin 2013a, b, 2014), therefore it may suffice here to give only a brief outline of the aspects relevant to our study.

The 3D-RISM approach operates with molecular-atom (site) spatial distribution functions (SDFs), $g_\alpha^{\mathrm{uv}}(\mathbf{r})$, which are the 3D-site (α) distribution functions of solvent (v) atoms around the solute (u) molecule. In the present case, an aqueous salt solution acts as the solvent for the amino acid so that the O and H atoms of water, as well as the inorganic ions, count as solvent sites, α. The SDFs describing ion-molecular association were obtained from the solute–solvent 3D-RISM integral equation (Kovalenko 2003) coupled with the 3D Kovalenko-Hirata (KH) closure (Kovalenko and Hirata 1999a, b). These SDFs were used to calculate the potential of mean force (PMF) as

$$W_\alpha^{\mathrm{uv}}(\mathbf{r}) = -k_{\mathrm{B}}T \ln g_\alpha^{\mathrm{uv}}(\mathbf{r}) \tag{1}$$

with k_{B} being Boltzmann's constant and T the Kelvin temperature. The PMF represents the ratio of the free energy of a solvent particle at a given distance from the solute to that in the bulk. The PMF is an energetic characteristic and a suitable tool to study possible ion-binding. It gives information on the stability of the formed ion-molecular associates (ion pairs) by the depth of the first minimum of the PMF. The depth of the first minimum corresponds to the height of the dominant peak of the SDF.

In our study the water–salt solutions of Ala-ZW were considered as a mixture of solvent (water molecules and inorganic ions) and solute (amino acid) with the common form of the interaction potential represented by the long-range electrostatic (Coulomb) and short-range Lennard-Jones (LJ) terms. In the framework of the used approximations, the solution under study is a molecular solution with rigid non-polarizable particles of solvent modeled as sets of atomic sites around the solute molecule (alanine). The corresponding LJ parameters were taken from the General Amber Force Field (GAFF) (Wang et al. 2004). For water the modified version of the SPC/E model (MSPC/E) was used (Lue and Blankschtein 1992). Solute-atom partial charges were calculated with the *antechamber* program from the AmberTools 1.4 package (Case et al. 2005) using the AM1-BCC method (Wang et al. 2006; Jakalian et al. 2000, 2002). The parameters for the optimized Ala-ZW structure (bond lengths and angles) were taken from Ref. (Kikuchi et al. 1997). As shown there, this structure corresponds to the most stable conformer of Ala-ZW in water. According to Ref. (Kikuchi et al. 1997), the energetic barrier between this conformer and other possible conformations is, at least, 1.6 kcal/mol (3 $k_{\mathrm{B}}T$). Therefore, the probability for of a salt-induced transition between the various conformers is low albeit this cannot be excluded.

Our calculations were carried out for one molecule of Ala-ZW in aqueous solutions of NaCl (salt concentrations $c = 0.5$–2 (3) M), KCl, $MgCl_2$(aq) and $CaCl_2$(aq)

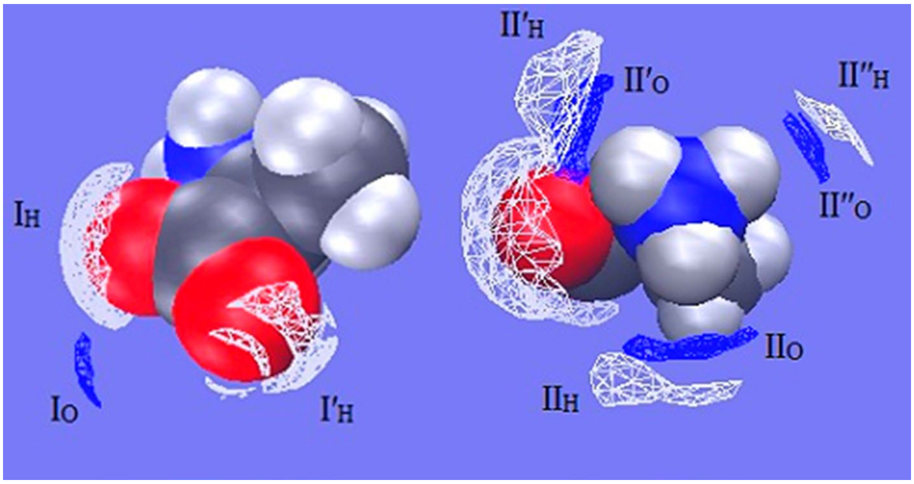

Fig. 2 Spatial distribution functions of water oxygens (*blue*) and water hydrogens (*white*) around the hydrophilic groups of Ala-ZW. The isodensity surfaces correspond to SDF values of $g_{\text{Ala-O}_\text{W}}(r) = 3.6$ (*blue*) and $g_{\text{Ala-H}_\text{W}}(r) = 3.8$ (*white*) (*left*); and (*right*) $g_{\text{Ala-O}_\text{W}}(r) = 4.8$ (*blue*) and $g_{\text{Ala-H}_\text{W}}(r) = 1.9$ (*white*) (color figure online)

(c = 0.5–2 M each) at ambient conditions using the NAB program (Luchko et al. 2010) from the AmberTools package (version 1.4) (Case et al. 2005). The numerical solution of the 3D integral equation was performed by the MDIIS (Modified Direct Inversion in the Iterative Subspace) iterative scheme (Kovalenko et al. 1999c). The efficiency of this scheme depends on the chosen set of special parameters such as the number of MDIIS vectors, the distance of the solute molecule from the boundary of solvent box, grid spacing in direct space, etc. The 3D-RISM-KH equations were solved on a 3D grid of 270 × 256 × 256 points with 5 MDIIS vectors and with a spacing of 0.025 nm in a parallelepiped cell of size 6.75 nm × 6.40 nm × 6.40 nm. Correspondingly, the distance from Ala-ZW to the boundary of solvent box was 3 nm. A residual tolerance of 10^{-6} was chosen. These parameters are large enough to accommodate the complex together with sufficient solvation space around it so that the obtained results are without significant numerical errors.

The RISM method gives realistic information both on the solution structure and on the ion-binding of amino acids (see, for instance, Fedotova and Dmitrieva 2013, 2014; Fedotova and Kruchinin 2012a, b, 2013a, 2014; Terekhova et al. 2015). As an additional illustration of the abilities of the 3D-RISM approach, we calculated the distribution of water molecules around Ala-ZW molecule, Fig. 2. This figure indicates that the hydrogen atoms of neighboring water molecules preferably direct towards the carboxylate group whereas the amino group interacts with the oxygen atoms. Interestingly, no H-bonding of the amino nitrogen with water is observed (Fig. 2). The solute-oxygen (water) SDF is useful to calculate the total hydration number by integration this SDF over the volume V_{hs} occupied by first hydration shell of solute, $n_{\text{tot}} = \rho_\alpha \int_{V_{\text{hs}}} g_\alpha^{\text{uv}}(\mathbf{r})\text{dV}$ (ρ_α is the average number density of water oxygens). Using the special approximation for the first hydration shell of the solute as a closed surface with arbitrary shape suggested by us in Ref. (Fedotova and Kruchinin 2013a), we obtained n_{tot} ~ 21 for Ala-ZW. This value is in agreement with the partial hydration numbers for functional groups of this amino acid obtained earlier by us (Fedotova and Dmitrieva 2013) in the framework of the 1D-RISM approach (Kovalenko 2003) with site–site (atom–atom) distribution functions. There, ~11 were found for the average number of water molecules close to methyl group, ~5 for amino group is, and ~6 for carboxylate group.

Results and discussion

The PMFs for Ala-ZW at different salt concentrations are displayed in Figs. 3 and 4. Characteristic values of the PMFs and SDFs are summarized in Table 1.

As expected from electrostatics, the investigated cations form pairs with the $-\text{COO}^-$ group, $(-\text{COO}^-{:}\text{Cat})_{\text{aq}}$, Cat = Na^+, K^+, Ca^{2+}, Mg^{2+}, whereas the chloride ion associates with the $-\text{NH}_3{}^+$ group, $(-\text{NH}_3{}^+{:}\text{Cl}^-)_{\text{aq}}$. Similar results were observed by us for Gly-ZW in water–salt solutions (Fedotova and Kruchinin 2012b, 2014). Indirect evidence for ion-molecular association between the charged groups of Ala and Na^+ or K^+ and Cl^- comes from the enthalpic pair interaction parameters calculated from calorimetric data (Lu 2004). Additionally, our result for $-\text{COO}^-$ group corroborated by experimental studies into the binding of Na^+ and K^+ to the carboxylate moiety of acetate and formate ions (Aziz et al. 2008; Uejio et al. 2008; Rahman et al. 2012a, b). In particular, in dielectric relaxation experiments with aqueous sodium carboxylate solutions (Rahman et al. 2012a, b) clear evidence was found for the association between Na^+ and the carboxylate group.

The obtained PMF values (Table 1; Figs. 3, 4) suggest that all formed ion pairs are weak and their stability decreases with salt concentration (ionic strength). As can be seen from Table 1, for the studied

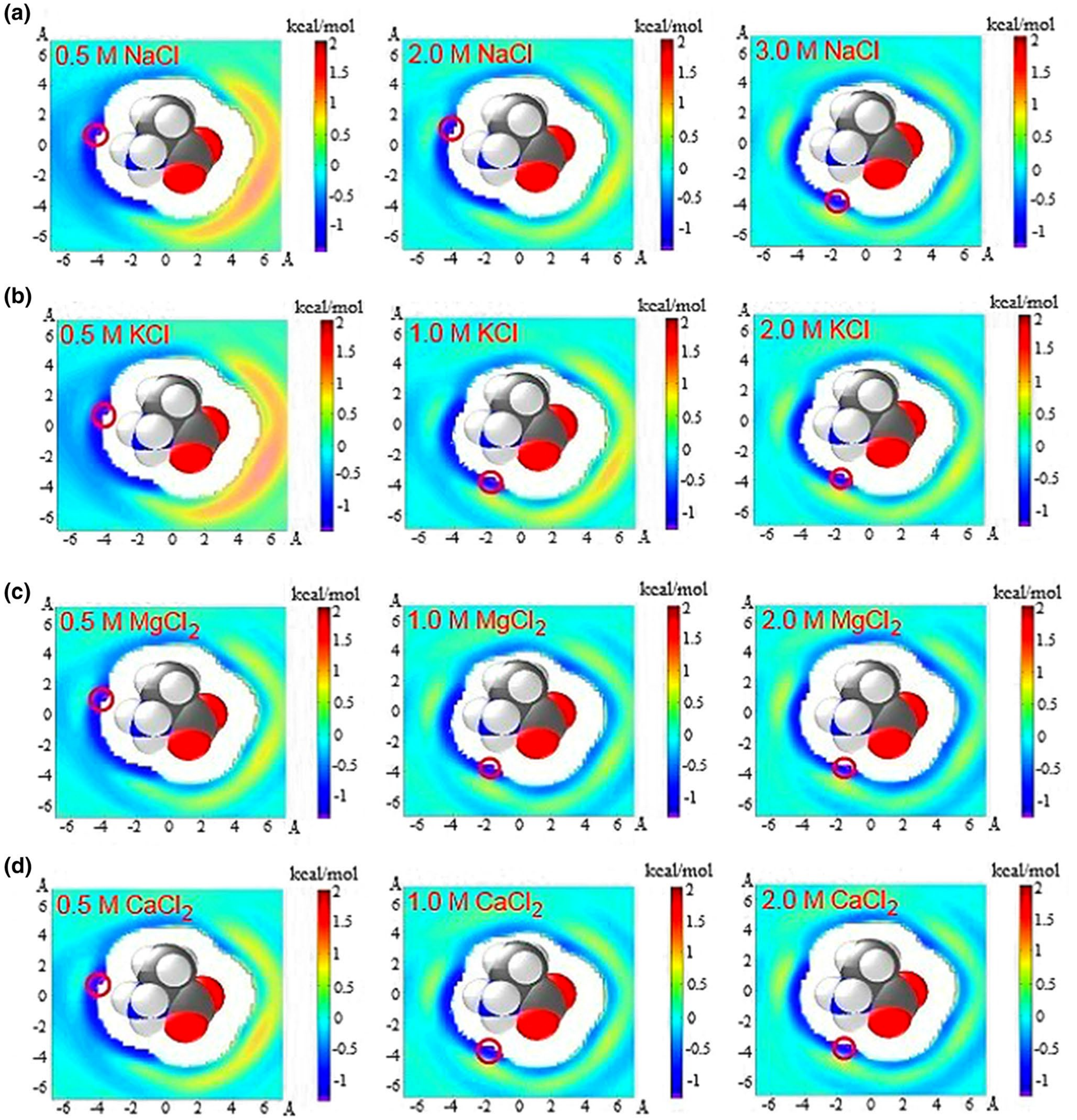

Fig. 3 Potentials of mean force between Ala-ZW and the anion in NaCl(aq) (**a**), KCl(aq) (**b**), $MgCl_2$(aq) (**c**), and $CaCl_2$(aq) (**d**) at different salt concentrations

cations the ion-pair stability decreases in the sequence $Mg^{2+} > Ca^{2+} > Na^{+} > K^{+}$. This series is similar to our data for Gly-ZW in water–salt solutions (Fedotova and Kruchinin 2014) and reflects the increasing affinity of these ions for water (Collins 2012). It confirms the calorimetric study (Lu 2004) where it was found that the enthalpic pair electrolyte–L-alanine interaction parameters decrease with the increases of the cationic radii. Moreover, our findings for the univalent ions are in agreement with conclusions from X-ray absorption spectroscopy (Aziz et al. 2008; Uejio et al. 2008), MD simulation and conductivity measurements (Vrbka et al. 2006). The latter investigation revealed stronger interaction of Na^{+} with the –COO^{-} group compared to K^{+}, as well as the formation of weak ion pairs

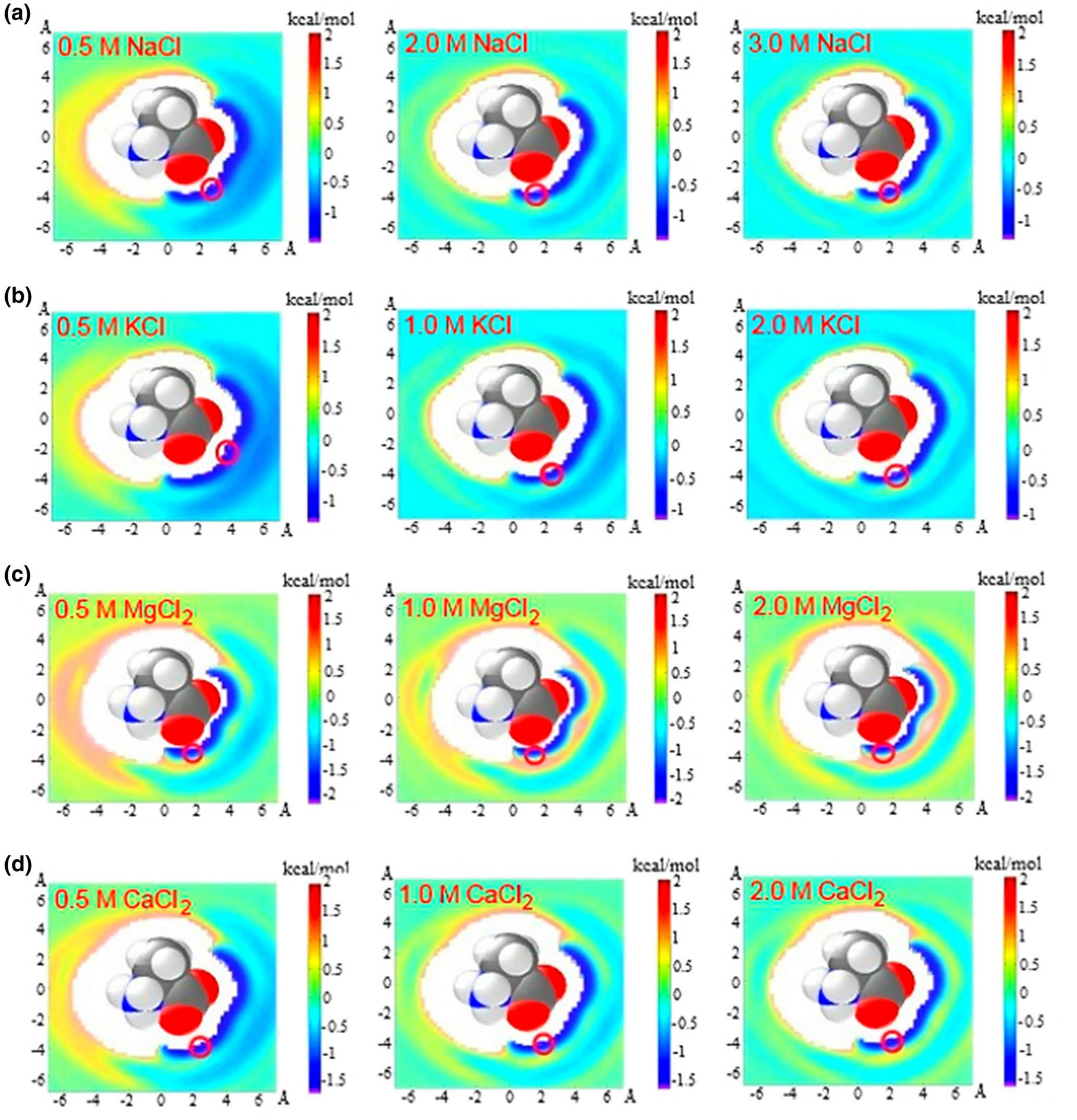

Fig. 4 Potentials of mean force between Ala-ZW and the cations in NaCl(aq) (**a**), KCl(aq) (**b**), $MgCl_2$(aq) (**c**), and $CaCl_2$(aq) (**d**) at different salt concentrations

$(COO^-{:}Na^+/K^+)_{aq}$ as a result of the ion-specific interaction. Also, the blue shift of the carbonyl feature in the X-ray absorption spectra of aqueous acetate solutions determined by Ref. (Uejio et al. 2008) suggests a preferential interaction of sodium versus potassium with the carboxylate moiety. As to the divalent cations, Mg^{2+} and Ca^{2+}, it is known (see Li 2006; Kummer et al. 2011 and references therein), that they are able to bind to active oxygen sites of proteins or peptides, suggesting already stronger interactions than for the alkali ions. More direct support for our findings comes from Collins (1997, 2004) where it was shown that Mg^{2+} interacts more strongly with the carboxylate moiety than Na^+ and K^+. A comparison with our data for Gly-ZW (Fedotova and Kruchinin 2014) shows that the stability of

Table 1 Characteristic values of the SDFs and PMFs for Ala-ZW in aqueous electrolyte solutions at different salt concentrations

Ion-molecular associate	Salt concentration			
	NaCl(aq)			
	0.5 M	1.0 M	2.0 M	3.0 M
$(\text{–COO}^{-}\text{:Na}^{+})_{aq}$				
PMF_{min}, kcal/mol	−1.46 (−1.48)	−1.42	−1.36	−1.30 (−1.33)
SDF_{max}	11.88	10.96	9.97	8.96
$(\text{–NH}_3^{+}\text{ :Cl}^{-})_{aq}$				
PMF_{min}, kcal/mol	−1.39 (−1.37)	−1.34	−1.28	−1.27 (−1.23)
SDF_{max}	10.50	9.85	8.70	8.00
	KCl(aq)			
	0.5 M	1.0 M	1.5 M	2.0 M
$(\text{–COO}^{-}\text{:K}^{+})_{aq}$				
PMF_{min}, kcal/mol	−1.28 (−1.26)	−1.13	−1.12	−1.11 (−1.12)
SDF_{max}	8.74	6.79	6.64	6.51
$(\text{–NH}_3^{+}\text{:Cl}^{-})_{aq}$				
PMF_{min}, kcal/mol	−1.39 (−1.32)	−1.25	−1.24	−1.23 (−1.22)
SDF_{max}	10.42	8.27	8.10	8.00
	$MgCl_2$(aq)			
	0.5 M	1.0 M	1.5 M	2.0 M
$(\text{–COO}^{-}\text{:Mg}^{2+})_{aq}$				
PMF_{min}, kcal/mol	−2.14 (−2.14)	−2.06	−2.05	−2.05 (−2.04)
SDF_{max}	37.42	32.30	31.73	31.72
$(\text{–NH}_3^{+}\text{:Cl}^{-})_{aq}$				
PMF_{min}, kcal/mol	−1.34 (−1.30)	−1.27	−1.27	−1.27 (−1.24)
SDF_{max}	9.55	8.57	8.55	8.55
	$CaCl_2$(aq)			
	0.5 M	1.0 M	1.5 M	2.0 M
$(\text{–COO}^{-}\text{:Ca}^{2+})_{aq}$				
PMF_{min}, kcal/mol	−1.70 (−1.70)	−1.63	−1.61	−1.61 (−1.60)
SDF_{max}	17.63	15.62	15.24	15.10
$(\text{–NH}_3^{+}\text{:Cl}^{-})_{aq}$				
PMF_{min}, kcal/mol	−1.32 (−1.28)	−1.26	−1.26	−1.25 (−1.22)
SDF_{max}	9.35	8.43	8.34	8.33

Our data for Gly-ZW (Fedotova and Kruchinin 2014) are shown in parentheses for comparison

all formed ion pairs for both amino acids is comparable (see Table 1).

At a given salt concentration the stabilities of the $(\text{–NH}_3^{+}\text{:Cl}^{-})_{aq}$ associates are similar for salts under study (Table 1). As it can be seen from Table 1, carboxylate-cation pairs are stronger than $(\text{–NH}_3^{+}\text{:Cl}^{-})_{aq}$ pairs except for $(\text{–COO}^{-}\text{:K}^{+})_{aq}$. Similar results were obtained by us for Gly-ZW in water–salt solutions (Fedotova and Kruchinin 2014) and also with MD simulations (Campo 2006), demonstrating that Na^{+} binds stronger to the –COO^{-} group than Cl^{-} to the –NH_3^{+} group.

Our results also show marked dependence of ion-molecular association on salt concentration (ionic strength). In 0.5–2.0 M NaCl(aq), as well as in 0.5 M KCl(aq), $CaCl_2$(aq), $MgCl_2$(aq), the Cl^{-} ion associates by interacting with the hydrogen atom of the ammonium group that is closest to the methyl group (Figs. 1, 3). However, for NaCl(aq) with $c \geq 3$ M and for KCl(aq), $CaCl_2$(aq), $MgCl_2$(aq) with $c \geq 1$ M Cl^{-} binding to ammonium is preferably via the hydrogen atom closest to the carboxylate group (Figs. 1, 3). For Gly-ZW such a change of the Cl^{-}-binding mode already occurs at lower salt concentrations

Table 2 A comparison of distances between inorganic ions with sum of their radii

Distances (nm) between the cation and anion calculated from the PMFs			
$r(Na^+–Cl^-)$	$r(K^+–Cl^-)$	$r(Mg^{2+}–Cl^-)$	$r(Ca^{2+}–Cl^-)$
0.277	0.318	0.337	0.304
Sum of the ion radii (nm)			
$0.095(Na^+) + 0.181(Cl^-) = 0.276$	$0.133(K^+) + 0.181(Cl^-) = 0.314$	$0.065(Mg^{2+}) + 0.181(Cl^-) = 0.246$	$0.099(Ca^{2+}) + 0.181(Cl^-) = 0.280$

(Fedotova and Kruchinin 2014), possibly due to less steric hindrance.

Let us now consider $(–COO^-:Cat^+)_{aq}$ complexes. According to Figs. 1 and 4, the aggregate adopts a conformation where one carboxylate oxygen atom is close to the $–NH_3^+$ group for all studied salt concentrations. The potassium ion is an exception. Up to 1 M K^+ binds to the carboxylate group of Ala-ZW by inserting itself between oxygen atoms of $–COO^-$ group, i.e. K^+ forms bifurcated (chelating) ion pairs. At higher *c* the conformation of the aggregate becomes similar to that of other studied salts (Fig. 4), namely, the cation binds via the carboxylate oxygen closest to the $–NH_3^+$ group. Possibly, this change of the ion-binding geometry of Ala-ZW in KCl(aq) revealed by our data (Figs. 3, 4) is connected with the peculiar solubility behavior of Ala in these solutions, namely the transition from a salting-in effect for the nonpolar moieties of the amino acid at low KCl concentration to an inverse dependence with salt concentration at high *c* (Ferreira et al. 2005).

The change in the interaction geometry of Ala-ZW (and especially of its ammonium moiety) with ions at high *c* is driven by the more compact solution structure. Our data suggest that at high *c* direct cation–anion pairs are formed which interact with Ala-ZW in such a way that quadrupolar aggregates are obtained. This is possible when the cation is displaced to the carboxylate oxygen closest to $–NH_3^+$ group and simultaneously Cl^- shifts to the amino hydrogen closest to $–COO^-$ group (see Fig. 1 for clarity). Obviously, increasing salt concentration leads to a competition between association of the inorganic ions and their binding to Ala-ZW. As a consequence, the stability of $(–COO^-:Cat)_{aq}$ and $(–NH_3^+:Cl^-)_{aq}$ ion pairs is reduced as can be seen from the less attractive PMF values (Table 1).

As can be supposed from the spatial distribution of the ions around Ala-ZW (Figs. 3, 4), all investigated cations form contact ion pairs (CIP) with Cl^-. This is suggested by the small anion–cation distances estimated from the corresponding PMFs which are similar to the sum of the ion radii (Table 2, the radii were taken from Cotton and Wilkinson (1988). We should note that in the case of Mg^{2+} there is some possibility for the formation solvent-shared ion pairs (SIPs) as the distance between Mg^{2+} and Cl^- is appreciably larger than the sum of their radii (Table 2). Our results are supported by literature data for corresponding alanine-free salt solutions. For instance, CIPs are formed between K^+ and Cl^- according to Gujt et al. (2014); Fennell et al. (2009); Waizutni et al. (1993) whereas Mg^{2+} and Cl^- can form SIPs according to Waizutni et al. (1993); Caminiti et al. (1979); Pàlinkàs et al. (1982). For pairs of Cl^- with Ca^{2+} or Na^+ it was shown (Gujt et al. 2014; Dang and Smith 1995; Chialvo and Somonson 2003; Megyes et al. 2004; Fennell et al. 2009) that CIPs are preferred at intermediate to high concentrations of salts.

Conclusions

We presented a 3D-RISM study of ion-molecular association of inorganic ions with the charged groups of Ala-ZW in biologically relevant aqueous salt solutions over wide salt concentration ranges. As expected, the inorganic cations Na^+, K^+, Mg^{2+}, and Ca^{2+}, are binding to the $–COO^-$ group, whereas Cl^- interacts with the $–NH_3^+$ group. However, all these pairs are weak, with the stability of the cation-carboxylate associates decreasing in the sequence $Mg^{2+} > Ca^{2+} > Na^+ > K^+$ and with increasing salt concentration (ionic strength). The same trend with concentration is also observed for $(–NH_3^+:Cl^-)_{aq}$ ion pairs but irrespective of the salt (i.e. cation) all studied systems exhibit similar stability at given *c*. The features of ion-molecular association obtained and discussed in the present manuscript are in qualitative agreement with the experimental findings available in literature. In particular, the present investigations revealed that the geometry of ion-binding changes with increasing salt concentration. This was traced back to the competing formation of inorganic ion pairs, leading to the formation of quadrupolar aggregates of Ala-ZW with the ion-pair.

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Conflict of interest The authors declare that they have no conflict of interest.

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