Biophysical Chemistry 190–191 (2014) 25–31

Contents lists available at ScienceDirect

Biophysical Chemistry

journal homepage: http://www.elsevier.com/locate/biophyschem

Ion-binding of glycine zwitterion with inorganic ions in biologically relevant aqueous electrolyte solutions

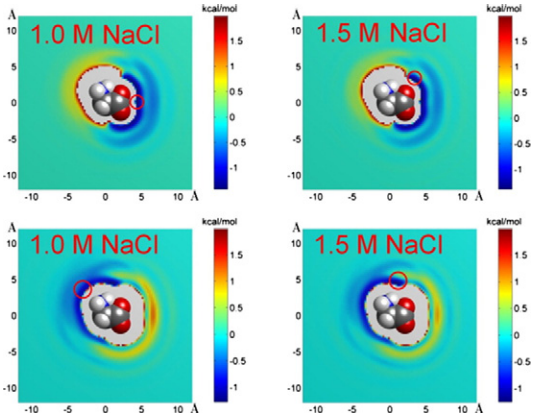
Marina V. Fedotova *, Sergey E. Kruchinin

G.A. Krestov Institute of Solution Chemistry, Russian Academy of Sciences, Akademicheskaya st., 1, 153045 Ivanovo, Russia

HIGHLIGHTS

- We study the ion-binding of Gly-ZW in NaCl(aq), KCl(aq), $MgCl_2^+$(aq), and $CaCl_2^+$(aq).
- Ion pairs between charged functional groups of Gly-ZW and inorganic ions are weak.
- The stability of ion pairs and influencing factors are considered.
- The features of ion-binding and salt concentration effect on it are discussed.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 7 February 2014
Received in revised form 2 April 2014
Accepted 2 April 2014
Available online 15 April 2014

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

ABSTRACT

The ion-binding between inorganic ions and charged functional groups of glycine zwitter-ion in NaCl(aq), KCl(aq), $MgCl_2$(aq), and $CaCl_2$(aq) has been investigated over a wide salt concentration range by using integral equation theory in the 3D-RISM approach. These systems mimic biological systems where binding of ions to charged residues at protein surfaces is relevant. It has been found that the stability of ion pairs formed by the carboxylate group and added inorganic cations decreases in the sequence $Mg^{2+} > Ca^{2+} > Na^+ > K^+$. However, all formed ion pairs are weak and decrease in stability with increasing salt concentration. On the other hand, at a given salt concentration the stability of $(-NH_3^+:Cl^-)_{aq}$ ion pairs is similar in all studied systems. The features of ion-binding and the salt concentration effect on this process are discussed.

1. Introduction

Ion-selective interactions of inorganic ions with protein surfaces play an important role in many chemical and biological processes occurring in aqueous solution. In particular, this is true for the interaction of cations with the anionic carboxylate groups as it influences protein association and enzymatic activity [1]. Recently, using computer simulations and conductivity measurements, Vrbka et al. [2] found a higher affinity of sodium over potassium ions for the protein surface. The authors claim that the stronger binding of Na^+ explains why Na^+ but not K^+ can impair the function of proteins in the cell. In recent years the effects of simple ions on proteins have been discussed on the base of the data from various methods (see, for instance, [2–9]) but so far a clear understanding of their molecular origin in complex biological systems has been elusive. One of the reasons for this situation is the necessity to

* Corresponding author. Tel.: +7 910 9882246; fax: +7 4932 336237.
E-mail address: hebrus@mail.ru (M.V. Fedotova).

http://dx.doi.org/10.1016/j.bpc.2014.04.001
0301-4622/

separate different effects originating from the many types of interactions in biomedia [10]. A more suitable way to study ion-selective interactions is to use simple model compounds with isolated functional groups, such as amino acids.

In the aqueous phase amino acids exist as zwitterions (ZW) bearing simultaneously charged ammonium and carboxylate moieties. In many biological systems they form complexes with alkali metals (Na^+, K^+) [11–15], copper I (Cu^+) [16,17] and copper II (Cu^{2+}) [16,17] or other ions [18] stabilizing the ZW. In particular, ab initio calculations [19] show this stabilization with Na^+ and Cl^-. This effect may be linked with the empirically established correlation between the tendency for contact ion-pair formation and the match between the hydration enthalpies of the complexing cations and the anionic carboxylate group [5,20,21]. In particular, the hydration enthalpy of Na^+ matches those of major intracellular anions or anionic groups, such as carboxylate, better than K^+. This conclusion has been confirmed by a recent investigation using XAS spectroscopy [14] and by a combined molecular dynamics and quantum chemical study [2]. Both revealed that sodium interacts more strongly with the COO^- group than potassium and that this ion-specific interaction is mediated by weak ion pairs $(COO^-{:}X^+)_{aq}$. However, the details and consequences of such ion-pairing on the molecular level are far from being fully understood.

In this paper we present the results of a statistical mechanics study of the ion-binding of glycine zwitterion (Gly-ZW) in biologically relevant electrolyte solutions, namely NaCl(aq), KCl(aq), $MgCl_2$(aq), and $CaCl_2$(aq), covering the wide salt-concentration range from near-physiological values to 2 M. The purpose is to mimic systems where ion pairing between charged basic groups at protein surfaces and physiologically relevant ions occurs. Fig. 1 shows a Gly-ZW molecule consisting of the charged hydrophilic $–COO^-$ and $–NH_3^+$ groups and the hydrophobic $–CH_2$ group. Gly was chosen as a biochemical model substance because of its simple molecular structure with the smallest possible hydrocarbon backbone. As a building block to many proteins and biologically active compounds, glycine also performs various important physiological functions. For example, the Gly-ZW can act as a neurotransmitter in the central nervous system [22], prevents ion-induced structural modifications of the intracellular chromatin [23–25], or provides the antacidic action (reduces the increased secretion of gastric juices). It is known, that glycine will not expose amino- and carboxyl groups at the protein surface. However, the ionic moieties on the protein surface are generally carboxylate and ammonium, and these groups may be close to each other as it is the case in the glycine molecule. Thus, glycine is a suitable model system to provide information on the hydration and ion-binding of such groups in a biological environment.

The last decades saw a significant growth in the number of studies for Gly-ZW in biologically relevant aqueous electrolyte solutions. Most of these papers are devoted to Gly-ZW hydration (see, for instance, [11,26–30]) but only a few investigations, generally restricted to monovalent cations [11,14,15,30], touched the problem of possible ion-binding of this amino acid. The aim of this paper is to study the features of ion-binding between inorganic ions, including divalent ones, and the charged functional groups of Gly-ZW and to elucidate the dependence of this process on salt concentration. To this end, we used the three-dimensional reference interaction site model (3D-RISM) integral equation theory to calculate the spatial(3D-) density distribution of solvent atoms (sites) in a local coordinate system linked to the solute molecule.

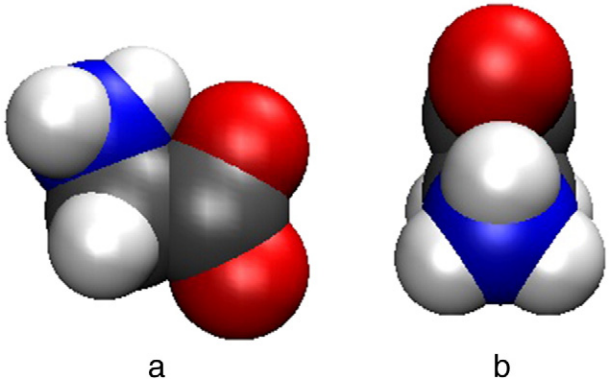


Fig. 1. Spatial configuration of Gly-ZW.

2. Theory and computational details

In the framework of integral equation theory (IET) of liquids the reference interaction site model (RISM), pioneered by Chandler and Andersen [31], is providing a realistic description of complex molecular liquids. The RISM method yields the structural and thermodynamic properties of solvents and solutions by taking into account their specific chemical features, like their intrinsic molecular structure or hydrogen bonding [32–34]. This approach is based on the solution of the one dimensional RISM (1D-RISM) IET, yielding the radial distribution functions (RDFs) associated with the atomic sites of the reference molecule in the liquid (see, for instance, [35–39]). Thus, 1D-RISM does not deal with the spatial correlations of solvent density around the solute. More detailed information on the solution structure, particular on the spatial distribution of the surrounding molecules, is provided by the 3D-version of the RISM (3D-RISM) IET. For the first time the idea of representation of the RISM distribution functions in three-dimensional space has been proposed by Chandler, McCoy and Singer for nonuniform polyatomic liquids [40,41]. Subsequently the 3D-RISM theory has been developed by Beglov and Roux [42,43], by Cortis, Rossky, and Freisner [44], by Kovalenko and Hirata ([45,46]) and mainly for non-charged, polar, and ionic molecular species in polar molecular solvents. Last decade 3D-RISM IET has been successfully used for study of the structure of biomolecules solutions [47–55]. As this method is described in detail elsewhere [46] it may suffice here to give only a brief outline of the aspects relevant for our study.

The 3D-RISM approach operates with molecular-atom (site) spatial distribution functions (SDFs), $g_\gamma^{uv}(r, \Omega) \equiv g_\gamma^{uv}(\mathbf{r})$, which are the 3D-site (γ) distribution functions of solvent (v) atoms around the solute (u) molecule. In the present case an aqueous electrolyte solution acts as the solvent for the amino acid so that the O and H atoms of water, as well as the inorganic (atomic) ions, count as solvent sites, γ. To obtain the SDF a solute molecule (namely, its center of mass or a specific site) is fixed at the origin of a local (spherical) reference frame and the local atomic densities of all γ are determined by computing both radial, r, and angular, $\mathbf{\Omega} = (\theta, \phi)$, coordinates of the site–site distance vector $\mathbf{r}$.

In this work the SDFs associated with ion binding were obtained from the solute–solvent 3D-RISM integral equation given in Ref. [46],

$$h_\gamma^{uv}(\mathbf{r}) = c_\alpha^{uv}(\mathbf{r}) * \left(\omega_{\alpha\gamma}^{vv}(r) + \rho_v h_{\alpha\gamma}^{vv}(r)\right), \quad (1)$$

where $h_\gamma^{uv}(\mathbf{r})$ and $c_\gamma^{uv}(\mathbf{r})$ are, respectively, the 3D-total and direct molecular-atom (site) correlation functions of solvent site γ (here the inorganic ion) around the solute molecule; $h_{\alpha\gamma}^{vv}(r)$ is the radial site-site total correlation function of the solvent, $\omega_{\alpha\gamma}^{vv}(r)$ is the intramolecular correlation function of the solvent, ρ_v is the average solvent density. The asterisk means convolution in direct space and summation over repeating indices. The SDF is defined by $g_\gamma^{uv}(\mathbf{r}) \equiv h_\gamma^{uv}(\mathbf{r}) + 1$.

To make Eq. (1) complete a closure relationship is required. We used the three-dimensional Kovalenko–Hirata closure (3D-KH) [56,57] which is given by

$$g^{uv}{}_\gamma(\mathbf{r}) = \begin{cases} \exp(d^{uv}{}_\gamma(\mathbf{r})), & d^{uv}{}_\gamma(\mathbf{r}) \le 0 \\ 1 + d^{uv}{}_\gamma(\mathbf{r}), & d^{uv}{}_\gamma(\mathbf{r}) > 0 \end{cases}, \quad (2)$$

$$d^{uv}{}_\gamma(\mathbf{r}) = -\beta U^{uv}{}_\gamma(\mathbf{r}) + h^{uv}{}_\gamma(\mathbf{r}) - c^{uv}{}_\gamma(\mathbf{r})$$

where $U^{uv}_{\gamma}(\mathbf{r})$, expressed by a sum of Coulomb and Lennard–Jones terms, is the interaction potential between site γ of the solvent molecule (here the ion) and the whole solute, $\beta = 1/k_BT$ with k_B being Boltzmann's constant and T is the Kelvin temperature.

The obtained SDFs were used to calculate the potential of mean force (PMF) as

$$W^{uv}_{\gamma}(\mathbf{r}) = -k_BT \ln g^{uv}_{\gamma}(\mathbf{r}) \quad (3)$$

which represents the ratio of the free energy of a solvent particle at a given distance from the solute to that in the bulk. As an energetic characteristic, the PMF is a suitable instrument for examining possible ion-binding and informs in the stability of the formed 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.

Our calculations were carried out for one molecule of Gly-ZW in aqueous solutions of NaCl (salt concentrations $c = 0.154$–2 M), KCl ($c = 0.158$–2(3) M), $MgCl_2$(aq) and $CaCl_2$(aq) ($c = 0.01$–2 M each) at ambient conditions using the NAB program [58] from the AmberTools package (version 1.4) [59]. The results of 1D-RISM calculations for the water-salt solution at finite concentrations were used as input data for the solvent to perform 3D-RISM calculations. The 3D-RISM-KH equations were solved on a 3D grid of 250 × 256 × 256 points with a spacing of 0.25 Å in a parallelepiped cell of size 62.5 Å × 64 Å × 64 Å. This was large enough to accommodate the complex together with sufficient solvation space around it. The numerical solution of the 3D integral equation was performed by combining Picard iterations and the MDIIS (Modified Direct Inversion in the Iterative Subspace) iterative scheme [60] with 5 MDIIS vectors; a residual tolerance of 10^{-6} was chosen.

Atom coordinates of the solute were adopted from the PubChem Structure DataBase [61]. Solute-atom partial charges were calculated with the *antechamber* program from the AmberTools 1.4 package [59] using the AM1-BCC method [62–64]. The corresponding LJ parameters were taken from the General Amber Force Field (GAFF) [62]. For water the modified version of the SPC/E model (MSPC/E) was used [65].

3. Results and discussion

Fig. 2 shows the calculated SDFs for Gly-ZW in NaCl(aq), $MgCl_2$(aq), and $CaCl_2$(aq) at $c = 2$ M, and in KCl(aq) at $c = 3$ M as examples. The PMFs for Gly-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 $-COO^-$ group, $(-COO^-{:}Cat)_{aq}$, Cat = Na^+, K^+, Ca^{2+}, Mg^{2+}, whereas the chloride ion associates with the $-NH_3^+$ group, $(-NH_3^+{:}Cl^-)_{aq}$. This result is clearly visible from the SDFs (Fig. 2) and corroborates MD simulations for Gly-ZW in NaCl(aq) [11], as well as experimental studies, using XAS [14], NEXAFS [9] or dielectric spectroscopy [66,67], into the binding of Na^+ and K^+ to the carboxylate group of glycine, acetate and formate. Indirect evidence for ion pair formation between the charged groups of Gly and Na^+ and Cl^- came also from the analysis of density, sound velocity and refractive index of water–glycine–NaCl systems [15].

The obtained values for the PMF (Table 1, Fig. 3) suggest that all formed ion pairs are weak and their stability decreases with salt concentration (ionic strength). For the studied cations the ion-pair stability decreases in the sequence $Mg^{2+} > Ca^{2+} > Na^+ > K^+$ which corresponds to the increasing affinity of these ions for water [6] and consistent with classic idea of field strength [68,69]. Our fndings for the monovalent ions are in agreement with conclusions from X-ray absorption spectroscopy [9,14], MD simulations and conductivity measurements [2]. The divalent cations, Mg^{2+} and Ca^{2+}, are known (see [70,71] and references therein) to bind to active oxygen sites of proteins and peptides, suggesting already stronger interactions than for the alkali ions. More direct support for our findings comes from Refs. [5,20,21] showing that Mg^{2+} ion interacts more strongly with the carboxylate moiety than both Na^+ and K^+.

Comparison of the PMF minimum values at the lowest and highest salt concentration (Table 1) indicates that the effect of ionic screening is larger for the salts with monovalent cations then for the salts with divalent cations. In this regard the changes of the PMF minimum values with rising salt concentration (Table 1) do not correlate with the changes of the Debye screening length appearing in simple continuum Poisson–Boltzmann (PB) approach. This arises because the PB approach cannot take into account details of the solvation structure of molecules as it deals with Coulomb interactions only and ignores the short-range interactions. As a result, continuum models based on the PB approach give only a rather poor prediction for the concentration dependence of the PMF, in particular, for the depth and location of the PMF minimum (see, for instance, Fig. 1 in Ref. [72]).

As it can be seen from the Table 1, at a given salt concentration the stabilities of the $(-NH_3^+{:}Cl^-)_{aq}$ ion pairs are similar for all salts. The possibility for direct Cl^- binding to amide groups of the protein backbone was considered in literature [73,74] but information on its strength is scarce. Our results (Table 1) suggest that, except for $(-COO^-{:}K^+)_{aq}$, carboxylate-cation pairs are stronger than $(-NH_3^+{:}Cl^-)_{aq}$ pairs. This is consistent with the inference from MD simulations showing that Na^+ is stronger bound to the $-COO^-$ group of Gly-ZW than Cl^- ion is bound to its $-NH_3^+$ [11].

An important result of our investigation is that the way of ion binding (the molecular interaction geometry according to Aziz et al. [14]) between the functional groups of Gly-ZW and the inorganic ions markedly depends on salt concentration (ionic strength). As can be seen from Fig. 3, up to $c \approx 1.5$–2 M of NaCl, KCl and $CaCl_2$ the cation forms bifurcated (chelating) ion pairs, i.e. it is embedded between the oxygen atoms of the $-COO^-$ group. Our results thus corroborate findings from

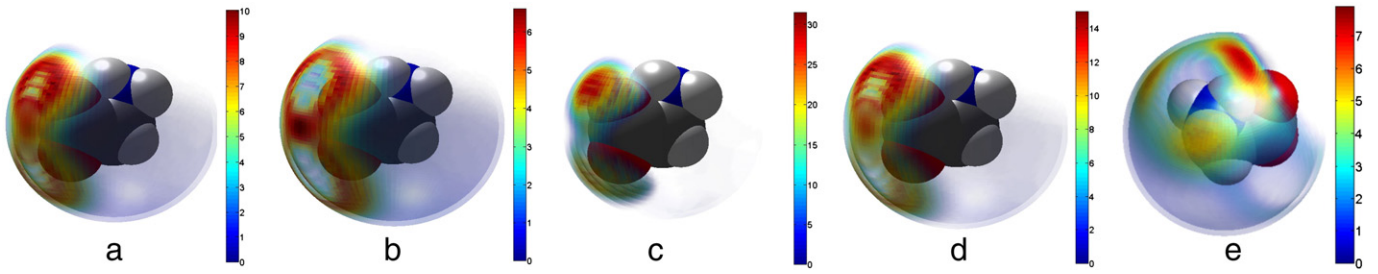


Fig. 2. Spatial distribution functions, $g^{uv}_{\gamma}(\mathbf{r})$, of the inorganic cations (Na^+, K^+, Mg^{2+},Ca^{2+}) around Gly-ZW in 2 M NaCl(aq) (*a*), 3 M KCl(aq) (*b*), 2 M $MgCl_2$(aq) (*c*), 2 M $CaCl_2$(aq) (*d*) and of the anion (Cl^-) around Gly-ZW in 2 M NaCl(aq) (*e*). The red areas indicate to the most probable location of the ions.

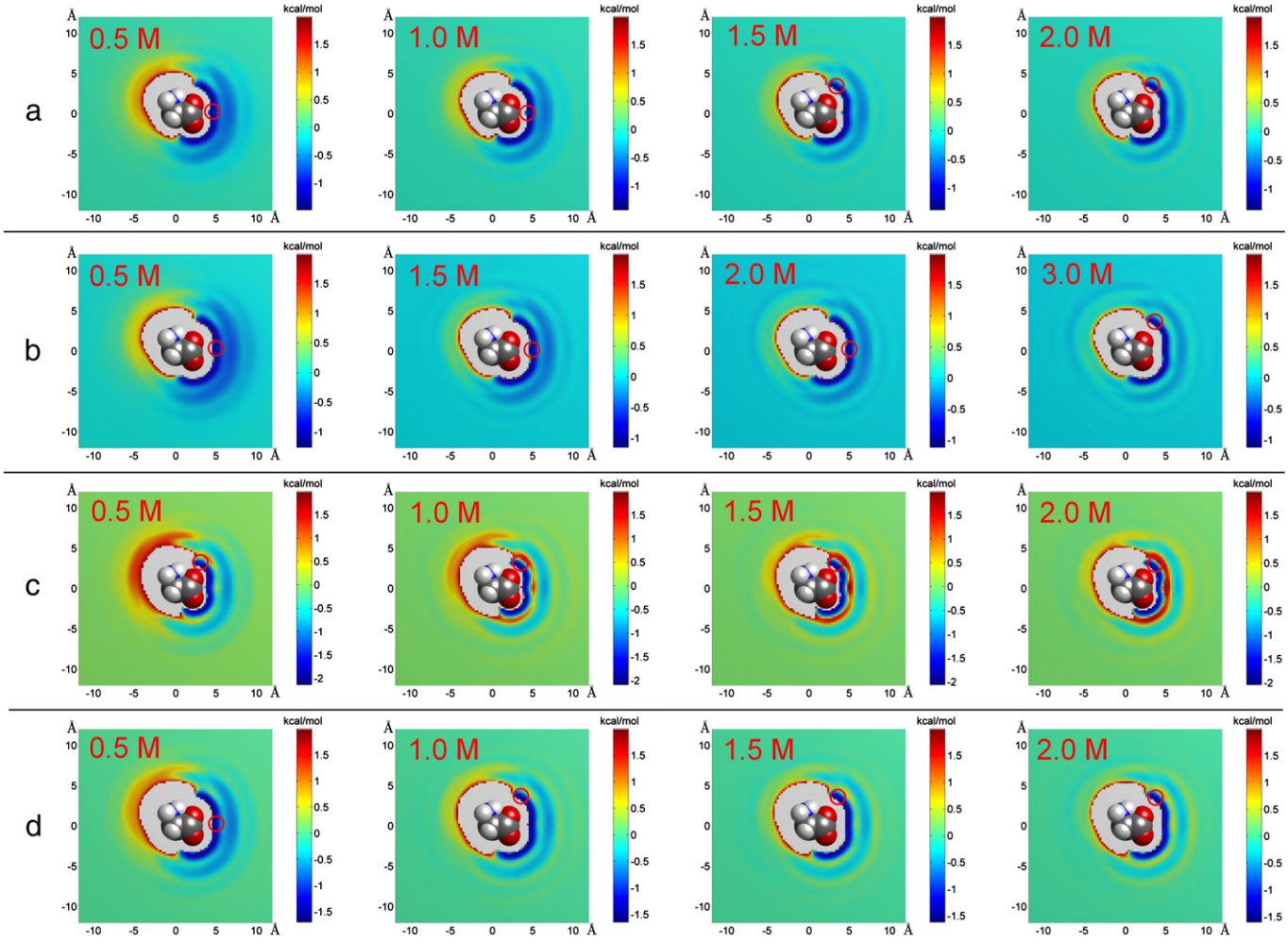


Fig. 3. Potentials of mean force between Gly-ZW and the cations in NaCl(aq) (*a*), KCl(aq) (*b*), $MgCl_2$(aq) (*c*), and $CaCl_2$(aq) (*d*) at different salt concentrations.

an XAS investigation [14] indicating that up to ~1 M alkali cations are observed to take middle position between the carboxylate oxygens. At higher salt concentrations Na^+, K^+ and Ca^{2+} pair with the $-COO^-$ group via the carboxylate oxygen closest to the $-NH_3^+$ group (Fig. 1a). This form of binding was observed for NaCl(aq) at $c > 1$ M, for KCl(aq) at $c > 2$ M and for $CaCl_2$(aq) at $c > 0.5$ M (Fig. 3). On the other hand, Mg^{2+} prefers to interact with the carboxylate oxygen closest to $-NH_3^+$ group over the entire salt concentration range, 0.01–2 M $MgCl_2$(aq). This is not only obvious from Fig. 3 but also clearly shows up in the Gly-ZW-cation SDFs of Fig. 2.

For all systems at near-physiological salt concentrations the anion, Cl^-, forms $(-NH_3^+{:}Cl^-)_{aq}$ ion pairs by interacting with the ammonium hydrogens furthest away from the $-COO^-$ group (Fig. 4, the PMFs at 0.154 M NaCl and 0.158 M KCl are not shown, & Fig. 1b). However, at higher c the anion preferably binds to hydrogen atom of $-NH_3^+$ that is closest to the carboxylate group (Fig. 4). For NaCl(aq) and KCl(aq) this change of the coordination geometry occurs at $c > 1$ M, whereas for $MgCl_2$(aq) and $CaCl_2$(aq) $c > 0.01$ M is already sufficient.

Ion binding is competing with the hydration of the charged moieties on Gly-ZW. It is thus interesting to know the corresponding interaction energies. For the $(-COO^-{-}H_W)$ complex the obtained values for the PMF between Gly-ZW and water (W) range from approximately −1.14 to 1.20 kcal/mol at near-physiological concentration of salts to ca. −1.00 kcal/mol at $c = 2$ M. For $(-NH_3^+{-}O_W)$ PMFs range from about −0.90 kcal/mol at near-physiological concentration of salts to ca. −0.84 kcal/mol at $c = 2$ M. Clearly, these values are smaller than the PMFs between Gly-ZW and the studied ions (Table 1) and indicate that direct (contact) binding of the ions to the charged hydrophilic groups of Gly-ZW is preferred.

Probably the change in the interaction geometry of Gly-ZW with cations when going from low to high concentrations is driven by the more compact solution structure at high c which results in the formation of direct cation-anion pairs that interact with Gly-ZW to form quadrupolar aggregates. This is possible when the cation is displaced to carboxylate oxygen closest to $-NH_3^+$ and simultaneously Cl^- shifts to the amino hydrogen closest to $-COO^-$ (see Fig. 1a for clarity). From the spatial distribution of the ions around Gly-ZW we can suppose that the cations and Cl^- form solvent-shared (SIP) or contact ion pairs (CIP) with almost certainly SIP for Mg^{2+} and CIP for K^+. This is supported by the distances between the ions estimated from the corresponding PMFs, $r(Na^+{-}Cl^-) = 3.41$ Å, $r(K^+{-}Cl^-) = 3.28$ Å, $r(Mg^{2+}{-}Cl^-) = 4.71$ Å, and $r(Ca^{2+}{-}Cl^-) = 3.01$ Å. Taking into account the ion radii ($R(Na^+) = 0.95$ Å, $R(K^+) = 1.33$ Å, $R(Mg^{2+}) = 0.65$ Å, $R(Ca^{2+}) = 0.99$ Å, $R(Cl^-) = 1.81$ Å [75]), the obtained r values are consistent with SIPs between Mg^{2+} and Cl^- and CIPs between Na^+, K^+, Ca^{2+} and Cl^-. Support for this inference comes from studies of the corresponding glycine-free electrolyte solutions which suggest that Mg^{2+} and Cl^- only form SIPs [76–79] whereas CIPs are formed between K^+ and Cl^- [80,81]. For pairs of Cl^- with Ca^{2+} or Na^+ both, contact and solvent-shared, configurations were invoked with CIPs preferably forming at intermediate to high c [80–84]. Obviously, increasing salt concentration leads to a competition between association of the salt ions and their binding to Gly-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, see Table 1.

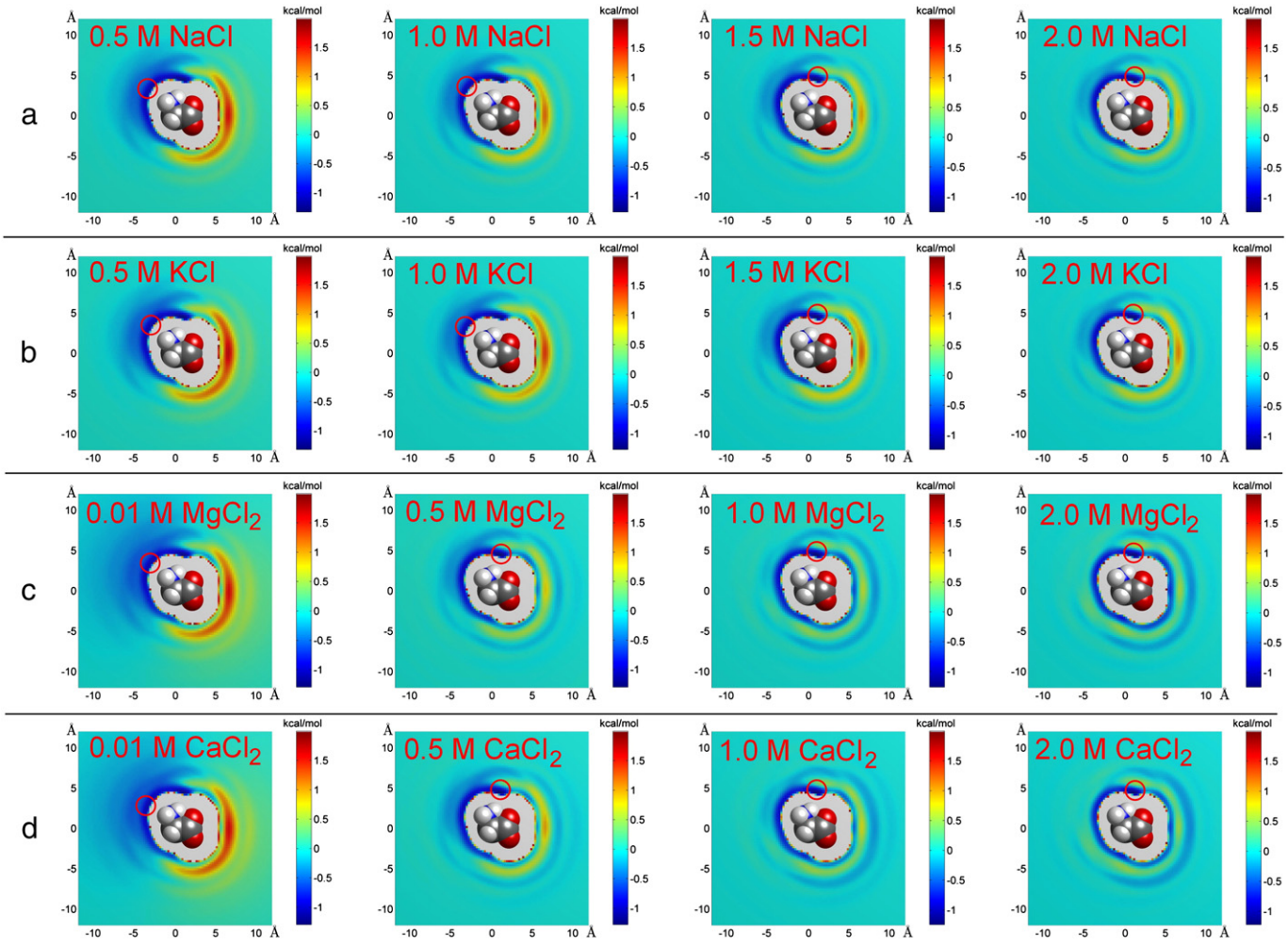


Fig. 4. Potentials of mean force between Gly-ZW and the anion in NaCl(aq) (*a*), KCl(aq) (*b*), $MgCl_2$(aq) (*c*), and $CaCl_2$(aq) (*d*) at different salt concentrations.

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

Ion pair	Salt concentration					
	NaCl(aq)					
		0.154 M	0.5 M	1.0 M	1.5 M	2.0 M
$(-COO^-:Na^+)_{aq}$	PMF_{min}, kcal/mol	−1.53	−1.48	−1.42	−1.39	−1.36
	SDF_{max}	13.23	12.31	11.11	10.44	10.02
$(-NH_3^+:Cl^-)_{aq}$	PMF_{min}, kcal/mol	−1.37	−1.33	−1.28	−1.26	−1.24
	SDF_{max}	10.06	9.50	8.69	8.37	8.14
KCl(aq)						
		0.158 M	0.5 M	1.0 M	1.5 M	2.0 M
$(-COO^-:K^+)_{aq}$	PMF_{min}, kcal/mol	−1.32	−1.26	−1.20	−1.15	−1.12
	SDF_{max}	9.22	8.44	7.54	6.99	6.63
$(-NH_3^+:Cl^-)_{aq}$	PMF_{min}, kcal/mol	−1.37	−1.32	−1.27	−1.24	−1.22
	SDF_{max}	10.18	9.38	8.57	8.13	7.88
$MgCl_2$(aq)						
		0.01 M	0.5 M	1.0 M	1.5 M	2.0 M
$(-COO^-:Mg^{2+})_{aq}$	PMF_{min}, kcal/mol	−2.17	−2.14	−2.09	−2.06	−2.04
	SDF_{max}	33.01	37.27	34.30	32.62	31.493
$(-NH_3^+:Cl^-)_{aq}$	PMF_{min}, kcal/mol	−1.30	−1.30	−1.27	−1.25	−1.24
	SDF_{max}	8.97	9.01	8.56	8.34	8.20
$CaCl_2$(aq)						
		0.01 M	0.5 M	1.0 M	1.5 M	2.0 M
$(-COO^-:Ca^{2+})_{aq}$	PMF_{min}, kcal/mol	−1.70	−1.70	−1.65	−1.62	−1.60
	SDF_{max}	17.79	17.71	16.15	15.43	14.99
$(-NH_3^+:Cl^-)_{aq}$	PMF_{min}, kcal/mol	−1.30	−1.28	−1.25	−1.23	−1.22
	SDF_{max}	8.96	8.71	8.21	8.01	7.90

4. Conclusions

Using the 3D-RISM theory we investigated the ion binding between inorganic ions and the charged groups of Gly-ZW in biologically relevant aqueous electrolyte solutions over wide salt concentration ranges. It was found that all studied ions, Na^+, K^+, Mg^{2+}, Ca^{2+}, and Cl^-, form weak ion pairs with $-COO^-$ respectively $-NH_3^+$. The stability of the cation–carboxylate pairs decreases 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 all studied systems exhibit similar stability at given *c*. Information on the coordination geometry was obtained. The observed change when going from near-physiological to concentrated solutions was traced back to competing ion-pair formation between the ions of the added salt, leading to the formation of quadrupolar aggregates.

Acknowledgments

This work was supported by funds from the Seventh Framework Program of the European Union (FP7-PEOPLE-2009-IRSES, Marie Curie Project) under grant agreement No. 247500 and by the Russian Foundation for Basic Research (grant No. 12-03-97508–r_centre_a).

References

[1] T.A. Waigh, *Applied biophysics:* a molecular approach for physical scientists, Wiley & Sons, Chichester, 2007.
[2] L. Vrbka, J. Vondrášek, B. Jagoda-Cwiklik, R. Vácha, P. Jungwirth, Quantification and rationalization of the higher affinity of sodium over potassium to protein surfaces, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 15440–15444.
[3] W. Kunz, J. Henle, B.W. Ninham, Zur Lehre von der Wirkung der Salze (About the science of the effect of salts): Franz Hofmeister's historical papers, Curr. Opin. Colloid Interface Sci. 9 (2004) 19–37.
[4] K. Collins, M. Washabaugh, The Hofmeister effect and the behaviour of water at interfaces, Q. Rev. Biophys. 18 (1985) 323–422.
[5] K.D. Collins, Ion hydration: implications for cellular function, polyelectrolytes, and protein crystallization, Biophys. Chem. 119 (2006) 271–281.
[6] K.D. Collins, Why continuum electrostatics theories cannot explain biological structure, polyelectrolytes or ionic strength effects in ion–protein interactions, Biophys. Chem. 167 (2012) 43–59.
[7] Y. Lu, Enthalpic interaction for a-amino acid with alkali metal halides in water, Chin. J. Chem. 22 (2004) 822–826.
[8] S.A. Hassan, Amino acid side chain interactions in the presence of salts, J. Phys. Chem. B 109 (2005) 21989–21996.
[9] J.S. Uejio, C.P. Schwartz, A.M. Duffin, W.S. Drisdell, R.C. Cohen, R.J. Saykally, Characterization of selective binding of alkali cations with carboxylate by X-ray absorption spectroscopy of liquid microjets, Proc. Natl. Acad. Sci. U. S. A. 105 (2008) 6809–6812.
[10] Y. Maréchal, The hydrogen bond and the water molecule: the physics and chemistry of water, aqueous and bio media, Elsevier, Amsterdam, 2007. (Chapter 10).
[11] M.G. Campo, Molecular dynamics simulation of glycine zwitterion in aqueous solution, J. Chem. Phys. 125 (2006) 114511–114518.
[12] T. Wyttenbach, J. Bushnell, M.T. Bowers, Salt bridge structures in the absence of solvent? The case for the oligoglycines, J. Am. Chem. Soc. 120 (1998) 5098–5103.
[13] B.A. Cerda, S. Hoyau, G. Ohanessian, C. Wesdemiotis, Na^+ binding to cyclic and linear dipeptides. Bond energies, entropies of Na^+ complexation, and attachment sites from the dissociation of Na^+-bound heterodimers and ab initio calculations, J. Am. Chem. Soc. 120 (1998) 2437–2448.
[14] E.F. Aziz, N. Ottosson, S. Eisebitt, W. Eberhardt, B. Jagoda-Cwiklik, R. Vacha, P. Jungwirth, B. Winter, Cation-specific interactions with carboxylate in amino acid and acetate aqueous solutions: X-ray absorption and ab initio calculations, J. Phys. Chem. B 112 (2008) 12567–12570.
[15] A. Soto, A. Arce, M.K. Khoskbarchi, Experimental data and modelling of apparent molar volumes, isentropic compressibilities and refractive indices in aqueous solutions of glycine + NaCl, Biophys. Chem. 74 (1998) 165–173.
[16] S. Hoyau, G. Ohanessian, Absolute affinities of α-amino acids for Cu^+ in the gas phase. A theoretical study, J. Am. Chem. Soc. 119 (1997) 2016–2024.
[17] J. Bertran, L. Rodriguez-Santiago, M. Sodupe, The different nature of bonding in Cu^+-glycine and Cu^{2+}-glycine, J. Phys. Chem. B 103 (1999) 2310–2317.
[18] S. Hoyau, G. Ohanessian, Interaction of alkali metal cations (Li^+–Cs^+) with glycine in the gas phase: a theoretical study, Chem. Eur. J. 4 (1998) 1561–1569.
[19] R.M. Minyaev, A.G. Starikov, V.I. Minkin, Stabilization of the glycine zwitterionic form by complexation with Na^+ and Cl^-: an *ab initio* study, Mendeleev Commun. 10 (2000) 43–44.
[20] K.D. Collins, Charge density-dependent strength of hydration and biological structure, Biophys. J. 72 (1997) 65–76.
[21] K.D. Collins, Ions from the Hofmeister series and osmolytes: effects on proteins in solution and in the crystallization process, Methods 34 (2004) 300–311.
[22] M. Wolff, In Burger's Medicinal Chemistry, 4th ed. Wiley, New York, 1979.
[23] S. Flock, R. Labarbe, C. Houssier, Osmotic effectors and DNA structure: effect of glycine on precipitation of DNA by multivalent cations, J. Biomol. Struct. Dyn. 13 (1995) 87–102.
[24] S. Flock, R. Labarbe, C. Houssier, ^{23}Na NMR study of the effect of organic osmolytes on DNA counterion atmosphere, Biophys. J. 71 (1996) 1519–1529.
[25] S. Flock, R. Labarbe, C. Houssier, Dielectric constant and ionic strength effects on DNA precipitation, Biophys. J. 70 (1996) 1456–1465.
[26] J.-J. Max, C. Chapados, Infrared spectroscopy of aqueous carboxylic acids: comparison between different acids and their salts, J. Phys. Chem. A 108 (2004) 3324–3337.
[27] Y. Kameda, H. Ebata, T. Usuki, O. Uemura, M. Misawa, Hydration structure of glycine molecules in concentrated aqueous solutions, Bull. Chem. Soc. Jpn. 67 (1994) 3159–3164.
[28] K. Sugawara, Y. Kameda, T. Usuki, O. Uemura, T. Fukunaga, Hydration structure of glycine molecules in aqueous alkaline solutions, Bull. Chem. Soc. Jpn. 73 (2000) 1967–1972.
[29] M.V. Fedotova, S.E. Kruchinin, Structural parameters of glycine zwitterion hydration from the data of the integral equation method in the RISM approach, Rus. J. Phys. Chem. A 86 (2012) 1828–1833.
[30] M.V. Fedotova, S.E. Kruchinin, 1D-RISM study of glycine zwitterion hydration and ion-molecular complex formation in aqueous NaCl solutions, J. Mol. Liq. 169 (2012) 1–7.
[31] D. Chandler, H.C. Andersen, Optimized cluster expansions for classical fluids. II. Theory of molecular liquids, J. Chem. Phys. 57 (1972) 1930–1937.
[32] J.P. Hansen, I.R. McDonald, Theory of Simple Liquids, third ed. Academic Press, New York, 2006.
[33] Molecular Theory of Solvation, in: F. Hirata (Ed.), Kluwer Academic Publishers, Dordrecht, 2003.
[34] M.V. Fedotova, M.F. Holovko, The integral equations method in equilibrium statistical theory of liquids, in: Theoretical and experimental methods of solution chemistry, Monograph in Russian(Prospect, Moscow, 2011. 68–152.
[35] M.V. Fedotova, Special features of structure formation of concentrated aqueous sodium chloride solution, Russ. J. Gen. Chem. 76 (2006) 1890–1897.
[36] M.V. Fedotova, S.E. Kruchinin, H.M.A. Rahman, R. Buchner, Features of ion hydration and association in aqueous rubidium fluoride solutions at ambient conditions, J. Mol. Liq. 159 (2011) 9–17.
[37] G.N. Chuev, M. Valiev, M.V. Fedotova, Integral equation theory of molecular solvation coupled with quantum mechanical/molecular mechanics method in NWChem package, J. Chem. Theory Comput. 8 (2012) 1246–1254.
[38] M.V. Fedotova, O.A. Dmitrieva, Structural parameters of alanine zwitterion hydration from the data of the integral equation method in the RISM approximation, Russ. Chem. Bull. 62 (2013).
[39] M.V. Fedotova, O.A. Dmitrieva, Hydration structure of $-NH_2^+$ and $-COO^-$ of L-proline zwitterion from data of 1D-RISM integral equation method, Russ. J. Phys. Chem. A 88 (2014) 794–797.
[40] D. Chandler, J.D. McCoy, S.J. Singer, Density functional theory of nonuniform polyatomic systems. I. General formulation, J. Chem. Phys. 85 (1986) 5971–5976.
[41] D. Chandler, J.D. McCoy, S.J. Singer, Density functional theory of nonuniform polyatomic systems. II. Rational closures for integral equations, J. Chem. Phys. 85 (1986) 5977–5982.
[42] D. Beglov, B. Roux, Numerical solution of the hypernetted chain equation for a solute of arbitrary geometry in three dimensions, J. Chem. Phys. 103 (1995) 360–364.
[43] D. Beglov, B. Roux, Solvation of complex molecules in a polar liquid: an integral equation theory, J. Chem. Phys. 104 (1996) 8678–8689.
[44] C.M. Cortis, P.J. Rossky, R.A. Friesner, A three-dimensional reduction of the Ornstein–Zernicke equation for molecular liquids, J. Chem. Phys. 107 (1997) 6400–6414.
[45] A. Kovalenko, F. Hirata, Three-dimensional density profiles of water in contact with a solute of arbitrary shape: a RISM approach, Chem. Phys. Lett. 290 (1998) 237–244.
[46] A. Kovalenko, Three-dimensional RISM theory for molecular liquids and solid–liquid interfaces, in: F. Hirata (Ed.), Molecular Theory of Solvation, Kluwer Academic Publishers, Dordrecht, 2003, pp. 169–276, (Chapt. 4, and references therein).
[47] T. Imai, A. Kovalenko, F. Hirata, Hydration structure, thermodynamics, and functions of protein studied by the 3D-RISM theory, Mol. Simul. 32 (2006) 817–824.
[48] T. Imai, R. Hiraoka, A. Kovalenko, F. Hirata, Water molecules in a protein cavity detected by a statistical–mechanical theory, J. Am. Chem. Soc. 127 (2005) 15334–15335.
[49] Q. Li, S. Gusarov, S. Evoy, A. Kovalenko, Electronic structure, binding energy, and solvation structure of the streptavidin–biotin supramolecular complex: ONIOM and 3D-RISM study, J. Phys. Chem. B 113 (2009) 9958–9967.
[50] D. Yokogawa, H. Sato, T. Imai, Sh. Sakaki, A highly parallelizable integral equation theory for three dimensional solvent distribution function: application to biomolecules, J. Chem. Phys. 130 (2009) 064111(1)–064111(6).
[51] K. Hirano, D. Yokogawa, H. Sato, Sh. Sakaki, An analysis of 3D solvation structure in biomolecules: application to coiled coil serine and bacteriorhodopsin, J. Phys. Chem. B 114 (2010) 7935–7941.
[52] Y. Maruyama, N. Yoshida, F. Hirata, Electrolytes in biomolecular systems studied with the 3D-RISM/RISM theory, Interdiscip. Sci. Comput. Life Sci. 3 (2011) 1–18.
[53] S. Phongphanphanee, N. Yoshida, F. Hirata, Molecular recognition explored by a statistical-mechanics theory of liquids, Curr. Pharm. Des. 17 (2011) 1740–1757.
[54] M.V. Fedotova, S.E. Kruchinin, The hydration of aniline and benzoic acid: analysis of radial and spatial distribution functions, J. Mol. Liq. 179 (2013) 27–33.
[55] M.V. Fedotova, S.E. Kruchinin, Hydration of para-aminobenzoic acid (PABA) and its anion—the view from statistical mechanics, J. Mol. Liq. 186 (2013) 90–97.
[56] A. Kovalenko, F. Hirata, Potential of mean force between two molecular ions in a polar molecular solvent: a study by the three-dimensional reference interaction site model, J. Phys. Chem. B 103 (1999) 7942–7957.

[57] A. Kovalenko, F. Hirata, Self-consistent description of a metal-water interface by the Kohn–Sham density functional theory and the three-dimensional reference interaction site model, J. Chem. Phys. 110 (1999) 10095–10112.
[58] T. Luchko, S. Gusarov, D.R. Roe, C. Simmerling, D.A. Case, J. Tuszynski, A. Kovalenko, Three-dimensional molecular theory of solvation coupled with molecular dynamics in Amber, J. Chem. Theory Comput. 6 (2010) 607–624.
[59] D.A. Case, T.E. Cheatham, T. Darden, H. Gohlke, R. Luo, K.M. Merz, A. Onufriev, C. Simmerling, B. Wang, R. Woods, The Amber biomolecular simulation programs, J. Comput. Chem. 26 (2005) 1668–1688 (http://www.ambermd.org/).
[60] A. Kovalenko, S. Ten-no, F. Hirata, Solution of three-dimensional reference interaction site model and hypernetted chain equations for simple point charge water by modified method of direct inversion in iterative subspace, J. Comput. Chem. 20 (1999) 928–936.
[61] E. Bolton, Y. Wang, P.A. Thiessen, S.H. Bryant, PubChem: integrated platform of small molecules and biological activities, Annu. Rep. Comp. Chem., 2008, pp. 217–241, (Washington DC,http://pubchem.ncbi.nlm.nih.gov/).
[62] J. Wang, R.M. Wolf, J.W. Caldwell, P.A. Kollman, D.A. Case, Development and testing of a general amber force field, J. Comput. Chem. 25 (2004) 1157–1174.
[63] A. Jakalian, B.L. Bush, D.B. Jack, C.I. Bayly, Fast, efficient generation of high-quality atomic charges. AM1-BCC model: I. Method, J. Comput. Chem. 21 (2000) 132–146.
[64] A. Jakalian, D.B. Jack, C.I. Bayly, Fast, efficient generation of high-quality atomic charges. AM1-BCC model: II. Parameterization and validation, J. Comput. Chem. 23 (2002) 1623–1641.
[65] L. Lue, D. Blankschtein, Liquid-state theory of hydrocarbon-water systems: application to methane, ethane, and propane, J. Phys. Chem. 92 (1992) 8582–8594.
[66] H.M.A. Rahman, G. Hefter, R. Buchner, Hydration of formate and acetate ions by dielectric relaxation spectroscopy, J. Phys. Chem. B 116 (2012) 314–323.
[67] H.M.A. Rahman, G. Hefter, R. Buchner, Hydration and sodium-ion binding of trifluoroacetate in aqueous solution, J. Mol. Liq. 176 (2012) 93–100.
[68] G. Eisenman, On the elementary atomic origin of equilibrium ionic specificity, in: A. Kleinzeller, A. Kotyk (Eds.), Symposium on Membrane Transport and Metabolism, Prague, Czechoslovak Academy of Science, Academic Press, New York, 1961, pp. 163–179.
[69] G. Eisenman, Cation selective glass electrodes and their mode of operation, Biophys. J. 2 (1962) 259–323.
[70] S.J. Li, Structural details at active site of hen egg white lysozyme with di- and trivalent metal ions, Biopolymers 81 (2006) 74–80.
[71] K. Kummer, D.V. Vyalikh, A. Bluher, V. Sivkov, V.V. Maslyuk, T. Bredow, I. Mertig, M. Mertig, S.L. Molodtsov, Real-time study of the modification of the peptide bond by atomic calcium, J. Phys. Chem. B 115 (2011) 2401–2407.
[72] A. Kovalenko, F. Hirata, Potentials of mean force of simple ions in ambient aqueous solution. II. Solvation structure from the three-dimensional reference interaction site model approach, and comparison with simulations, J. Chem. Phys. 112 (2000) 10403–10417.
[73] M.C. Vaney, I. Broutin, P. Retailleau, A. Douangamath, S. Lafont, C. Hamiaux, T. Prange, A. Ducruix, M. Ries-Kautt, Structural effects of monovalent anions on polymorphic lysozyme crystals, Acta Crystallographica, Section D, Biol. Crystallogr. 57 (2001) 929–940.
[74] D. Lamb, A.W. Schuttelkopf, D.M.F. van Aalten, D.W. Brighty, Charge-surrounded pockets and electrostatic interactions with small ions modulate the activity of retroviral fusion proteins, PLoS Pathog. 7 (2011) e1001268.
[75] F.A. Cotton, G. Wilkinson, Advanced Inorganic Chemistry, John Wiley and Sons, New York, 1988.
[76] R. Caminiti, G. Licheri, G. Piccaluga, G. Pinna, X-ray diffraction study of $MgCl_2$ aqueous solutions, J. Appl. Crystallogr. 12 (1979) 34–38.
[77] G. Pàlinkàs, T. Radnai, W. Dietz, Gy.I. Szàz, K. Heinzinger, Hydration shell structure in $MgCl_2$ solution from X-ray and MD studies, Z. Naturforsch. 37a (1982) 1049–1060.
[78] W. Dietz, W.O. Riéde, K. Heinzinger, Molecular dynamics simulation of an aqueous MgCl2 solution. Structural results, Z. Naturforsch. 37a (1982) 1038–1048.
[79] K. Waizutni, H. Masuda, N. Fulcushima, A molecular approach to the formation of KC1 and $MgCl^+$ ion-pairs in aqueous solution by density functional calculations, Chem. Phys. Lett. 205 (1993) 317–323.
[80] J. Gujt, M. Bešter-Rogač, B. Hribar-Lee, An investigation of ion-pairing of alkali metal halides in aqueous solutions using the electrical conductivity and the Monte Carlo computer simulation methods, J. Mol. Liq. 190 (2014) 34–41.
[81] C.J. Fennell, A. Bizjak, V. Vlachy, K.A. Dill, Ion pairing in molecular simulations of aqueous alkali halide solutions, J. Phys. Chem. B 113 (2009) 6782–6791.
[82] T. Megyes, T. Grosz, T. Radnai, I. Bakà, G. Pàlinkàs, Solvation of calcium ion in polar colvents: an X-ray diffraction and ab initio study, J. Phys. Chem. A 108 (2004) 7261–7271.
[83] L.X. Dang, D.E. Smith, Comment on “Mean force potential for the calcium-chloride ion pair in water”, J. Chem. Phys. 102 (1995) 3483–3484.
[84] A.A. Chialvo, J.M. Simonson, The structure of $CaCl_2$ aqueous solutions over a wide range of concentration. Interpretation of diffraction experiments via molecular simulation, J. Chem. Phys. 119 (2003) 8052–8061.