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RESEARCH NOTE

Molecular dynamic simulations of glycine amino acid association with potassium and sodium ions in explicit solvent [version 1; peer review: 1 approved with reservations]

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Abstract

Salt solutions are the natural environment in which biological molecules act, and dissolved ions are actively involved in biochemical processes. With metal ions, the membrane potentials are maintained. Ions are crucial for the activity of many enzymes, and their ability to coordinate with chemical groups modulates protein-protein interactions. Here we present a comparative study of sodium and potassium coordination with zwitterionic glycine, by means of explicit solvent molecular dynamics. We demonstrated that contact ion pair of cations and carboxylate group splits into two distinct coordination states. Sodium binding is significantly stronger than for potassium. These results can shed light on the different roles of sodium and potassium ions in abiogenic peptide synthesis.

Keywords

Potassium ion, sodium ion, ion pairing, molecular dynamics, ion coordination

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Any reports and responses or comments on the article can be found at the end of the article.

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Introduction

Salt solutions are the natural environment in which biological molecules act. Moreover, the dissolved ions themselves largely participate in many biological processes on a molecular level. Metal ions are essentially cofactors of many enzymes and may coordinate with charged groups, thus modulating protein-protein interactions and their activity¹. Many of these manifestations are due to specific ion coordination with charged groups on protein surfaces and other counterions in solutions, rather than the alteration of the aqueous solution structure in the bulk². Such ion - counterion pairing has been validated experimentally, and described theoretically using molecular simulations³.

Despite apparent similarity, the biological roles of sodium and potassium are very different. For example, the potassium to sodium ion concentration ratio is high inside the cell and low outside, which gives rise to membrane potentials. These two vital ions also demonstrate different catalytic capacity in the model reaction of prebiotic peptide synthesis, where potassium shows a higher activity⁴. In addition, their roles in abiogenesis are of high interest⁵.

It was supposed that sodium binds to charged groups on protein surfaces more strongly than potassium does, which probably correlates with the “salting out” sodium effect on proteins, and “salting in”, as is known for potassium⁶. Using an X-ray absorption study of solutions containing dissolved ions and acetate or glycine molecules, it was demonstrated that sodium has superior affinity to carboxylate, one of the major anionic groups in proteins⁷. In a number of works, such a difference was explained using a combination of molecular dynamics and *ab initio* calculations^{6–9}. With this method, the difference between sodium and potassium ion association free energies with carboxylate groups has been calculated⁹.

Using molecular dynamics, it was demonstrated that not only direct ion - carboxylate pair but also the solvent shared ion - carboxylate paired configurations are of great importance^{10–12}. Particularly, these solvent-mediated states appear more populated than direct contact ion pair, and can determine the thermodynamics of acetate salt solutions¹⁰. A number of *ab initio* calculations of ion coordination with amino acids in gas-phase were conducted previously^{13–15}; however solvent effects are significant and should be taken into account^{10,16,17}.

To better understand the molecular details of ion pairing on protein-protein interactions, the spatial distribution of ion positions is of interest. Here we present a molecular dynamic study of the spatial distribution of sodium and potassium coordinated with zwitterionic glycine in a concentrated water ionic solution.

Simulation details

Molecular dynamic (MD) simulations were conducted in GROMACS package (version 4.6.7)¹⁸. Simulation systems contained one zwitterionic glycine molecule (as at pH 7 it is the most probable glycine form in solution), 33 cations, 33 chloride anions and about 800 water molecules in a cubic periodic box with 3 nm sides, corresponding to a 2 M salt solution. Equilibration of 10 ns preceded 500 ns production MD for each system with constant

number of particles (N), constant pressure (P) and temperature (T) conditions – in NPT ensemble. Temperature at 300 K and pressure at 1 bar were maintained with Nose-Hoover thermostat^{19,20} and Parrinello-Rahman barostat²¹. Electrostatics PME method was used²² with grid spacing of 0.12 nm and 1.0 nm cutoff, the same as for van der Waals interactions. For zwitterionic glycine, parameters were from OPLS-AA force field²³, all bonds were constrained with LINCS algorithm²⁴ (for more details on parameters see run input files available in Dataset 1). Parameters for cations were obtained from 25, for chloride from 26 and a TIP3P water model was used²⁷. Radial distribution functions were calculated with bin width of 0.004 nm using *g_rdf* utility of GROMACS package. Spatial distribution were calculated with *g_spatial* GROMACS utility after least square fit of heavy atoms of glycine molecule from each frame to the position of starting MD structure.

Dataset 1. Run input parameters for production MD in GROMACS version 4.6.7

<http://dx.doi.org/10.5256/f1000research.10644.d149764>

Dataset 2. Input typologies and equilibrated structures for production MD (in zipped file)

<http://dx.doi.org/10.5256/f1000research.10644.d149765>

Results and discussion

Two systems were investigated, each consisted of one glycine dissolved in explicit water with sodium and chloride ions, or potassium and chloride ions. Radial distribution functions (RDF) of Na⁺ or K⁺ with respect to oxygen atoms or carbon atoms of glycine carboxylate group were calculated and are plotted in Figure 1 The O-Me⁺ RDF for both studied ions shows several coordination shells with a pronounced first maximum that is considerably higher for sodium, which lies in agreement with previous studies indicating a superior Na⁺ affinity^{6,7,10,12,17}. Analysis of C-Me⁺ RDF, however, is not so common in the literature. C-Me⁺ RDFs are plotted in Figure 1B, and show two sharp peaks for sodium ions at 0.28 and 0.34 nm, as well as two weaker separate, but distinct peaks for potassium at 0.32 and 0.36 nm. This figure indicates that there are two favorable coordination states of cations with carboxylate groups which both contribute to the single first peak of O-Me⁺ RDFs.

Figure 2 shows the iso-density surfaces of sodium or potassium ions calculated around glycine and explicitly reveals these coordination states. One sees the medial (*m*) coordination state equidistant from the oxygen atoms of the carboxylate group, and the lateral (*l*) state consisting of the two regions being closer to one of the two oxygen atoms. The asymmetry that is seen in the shape of the (*l*) state regions, including a bridge connecting the (*m*) and (*l*) in the case of K⁺, occurs due to positively charged NH₃ group and overall conformational flexibility of glycine. Density levels on the spatial distribution for sodium considerably exceed that for potassium, and during the simulations we occasionally observed only for sodium glycine coordinated with two ions in (*m*) and (*l*) states simultaneously (see Figure 3). Distances depicted in Figure 3

Figure 1. Radial distribution functions (RDF). (A) O-Me⁺ RDF, (B) C-Me⁺ RDF. Green, sodium; violet, potassium.

Figure 2. Spatial ion distributions. Iso-density surfaces around glycine are shown for Na⁺ (A and B) and K⁺ (C and D). Note that the density value (cutoff) for Na⁺ is much higher than for K⁺.

Figure 3. Trajectory snapshot of glycine coordinated with two sodium ions in (*m*) and (*l*) states simultaneously. Distances are given in nanometers. Green, sodium atoms; red, oxygen; gray, carbon; water molecules not shown.

clearly illustrate that the (*m*) state is closer to the C of carboxylate group and corresponds to the first peak on C-Me⁺ RDF (0.28 nm for Na⁺). The (*l*) state corresponds to the next peak (0.34 nm after minimum at 0.3 nm for Na⁺), while both states belong to the same peak of O-Me⁺ RDF (0.23 nm for Na⁺). In sodium simulation, glycine exists with Na⁺ in (*m*) coordinated state for 21% of the observation time and with Na⁺ solely in (*l*) coordinated state for 30%. For potassium simulation, we obtained 8% and 18% of time for (*m*) and (*l*) coordinated states, respectively.

Dataset 3. MD trajectories (.xtc) and input files (.tpr) for NaCl and KCl systems (in zipped file). Positions of water molecules are not included

<http://dx.doi.org/10.5256/f1000research.10644.d149766>

Conclusions

We demonstrated that contact ion pair of carboxylate group with Na⁺ or K⁺ splits into distinct, well occupied, (*m*) and (*l*) coordination states. The effect may be of interest in studies devoted to *ab initio* calculations and in the interpretation of X-Ray absorption data, as they account for (*m*) coordination state only⁶⁻⁸. Coordination with ions is thought to be crucial in the first stage of abiogenic peptide polymerization process²⁸ and therefore, the observed differences in sodium and potassium behavior are important for research into primary abiogenic peptide synthesis conditions.

Data availability

Dataset 1: Run input parameters for production MD in GROMACS version 4.6.7. doi, [10.5256/f1000research.10644.d149764](https://doi.org/10.5256/f1000research.10644.d149764)²⁹

Dataset 2: Input typologies and equilibrated structures for production MD (in zipped file). doi, [10.5256/f1000research.10644.d149765](https://doi.org/10.5256/f1000research.10644.d149765)³⁰

Dataset 3: MD trajectories (.xtc) and input files (.tpr) for NaCl and KCl systems (in zipped file). Positions of water molecules are not included. doi, [10.5256/f1000research.10644.d149766](https://doi.org/10.5256/f1000research.10644.d149766)³¹

Author contributions

Designed the setup of the simulation: IT SK SV VB MD. Conducted

simulations: IT. Analyzed the data: IT SK SV VB MD. Wrote the manuscript: IT SK VB MD.

Competing interests

No competing interests were disclosed.

Grant information

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In the present molecular dynamics simulation study, the authors are intended to study ion-pair formation of sodium and potassium ions with amino acid glycine. The manuscript is well written. However, major revision of the manuscript along the lines mentioned below is required before its publication.

Specific points are as follows:

1. The authors have used Na⁺ Force Field parameters from Ref. 25, in which (most probably) the interaction parameters for ions have been calculated from free energy calculation in SPC water. However, in the present case the authors have used TIP3P water. Isn't it right to use the same water model as the one used for deriving the parameters?
2. The motivation of the present study is to compare ion-pair formation of an amino acid carboxylate with Na⁺ and K⁺ ions in the physiological condition. What is the concentration of sodium or potassium ion in the physiological condition? Are the simulations performed under the same concentration?
3. Rather than considering two ions in two separate simulations, it is important to consider a mixture of two ions in a single simulation and compare relative affinity of these two ions towards the amino acid.
4. Why is glycine considered? It is already shown (Ref 6) that carboxylic acid groups of aspartate and glutamate are playing the most important role in determining the interaction of a protein with these ions. Therefore, choice of glycine instead of the above mentioned amino acids needs to be justified. I feel in order to get a trend, the author should take more than one amino acids in separate simulation and observe if the trend is general.
5. I did not understand the conditions for which Figs. 2(A) and (B) (or (C) and (D)) are shown. Please specify it in figure caption as well as in main text.

6. It is essential to find out the residence time of each of the ions and compare them.
7. Why in case of carbon-ion $g(r)$ the first peak splits into two, but not in case of oxygen-ion $g(r)$?
8. Trajectory snapshot as presented in Fig. 3 has no meaning in a finite temperature MD simulation run. Instead, please provide either average values of these distances or their time dependent behavior.
9. The authors have mentioned that X-Ray absorption data account for (m) coordination state only. However the present simulation shows both m and l states. Rationalize why the present result is different from the experimental result?
10. The authors have written "Parameters for cations were obtained from 25, for chloride from 26". Please write Ref. 25 in place of 25 and Ref. 26 in place of 26.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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