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BINDING FREE ENERGIES OF DIVALENT CATIONS TO FUNCTIONAL GROUPS OF AMINO ACIDS WITH OPLS-AA FORCE FIELD

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Purification of water from heavy metal ions is an urgent environmental problem. An actively studied method for this is the binding of metal ions by means of natural materials like plant proteins, as well as engineered materials like functionalized carbon allotropes. Carboxyl, thiol, amino groups are capable of complexing with metal cations, which leads to the removal of pollutants from water. Computational chemistry methods including classical molecular dynamics modeling are actively used in search of suitable materials. The paper evaluates the correctness of reproducing binding free energies of a number of divalent metal cations with functional groups found in amino acids using OPLS-AA force field. Both standard built-in and recently used potential models of cations are considered. Comparisons are made with respect to experimentally measured stability constants of modeled complexes or their structural analogues. Calculations of free energies are performed by the method of alchemical transformation. It is shown that despite the validity of the potential models, the binding free energies to functional groups of amino acids are generally poorly reproduced: strongly overestimated for the carboxylate group, underestimated for the thiolate and amino groups, and incorrect for imidazole. This indicates that OPLS-AA force field should be used with caution for calculation of the energy characteristics of metal binding. The way to fix potential models in order to accurately reproduce experimental values is outlined and applied to four cation – ligand complexes.

Keywords: *free energy, molecular dynamic simulation, protein macromolecule, heavy metals, stability constant of complex.*

Introduction

Divalent and polyvalent metal ions is an object of continuous investigation. Among the variety of reasons, their physiological activity is to be mentioned. On the one hand, some metals have essential biological roles, e.g. Cu^{2+} and Zn^{2+} serve as cofactors in enzymes. On the other hand, the so-called heavy metal ions constitute an important group of water pollutants. In general, this group includes ions of metal elements with high density, molar mass and atomic number, in particular Cu, Cd, Sn, Hg, Pb. Upon entering animals and humans even in low amounts they can cause a wide range of pathologies. At the same time, due to the functioning of industrial facilities, especially in emergency situations, these metals can enter natural waters and then drinking water or food. This justifies the urgency of the problem of purifying water from heavy metal ions. [1,2]

A promising and actively studied method is the use of proteins present in plant materials to bind these ions. Firstly, due to the presence of carboxyl, peptide, thiol groups etc., protein macromolecules are able to form complex compounds with metal ions as ligands. Secondly, if the macromolecule has a net negative charge, metal cations are adsorbed in the electric double layer of the protein. [3] In general, the ability of a protein to bind metals depends on its amino acid composition and spatial structure. Due to the low concentration of metal ions in polluted waters, the experimental determination of binding characteristics requires the use of analytical methods with a sufficiently low limit of detection. In addition, understanding the binding process at the molecular level will facilitate the selection of proteins for this task. This emphasizes the feasibility of using computational chemistry methods to study the problem.

Currently, molecular docking and classical molecular dynamics modeling methods are actively used to study the binding of metal ions by protein macromolecules. The geometry of the complexes is reproduced, it is possible to predict the influence of bound metals on the spatial structure of the macromolecule, and compare the binding ability of different cations. [4,5] However, an issue of fundamental importance is the possibility to calculate energy characteristics of the process, since it is the change in

free energy upon binding that is the key characteristic that determines binding constants, ion exchange constants, and other experimentally observed quantities.

This work is the continuation of the previous research on the topic. [6] There, the problem was considered from a general perspective. Namely, binding of individual functional groups of natural amino acids with heavy metal cations was investigated. The method of choice was classical molecular dynamics simulation with explicit solvent; a set of novel potential models for metal cations developed within AMBER force field was under validation. Rather poor match between predicted and experimental binding free energies was found for all studied functional groups.

Here, that study is advanced by considering another popular force field, namely, Optimized Potentials for Liquid Simulations – All-Atom (OPLS-AA). While AMBER is optimized for biomolecules, OPLS-AA is often chosen for multifarious organic materials, in particular carbon allotropes and their derivatives. [7–12] Several potential models of metal cations are validated, which were recently employed in a number of studies. This includes models of such essential contaminants as Cd^{2+}, Hg^{2+}, Pb^{2+}, which were not examined in the previous work. It will be shown that calculated values of binding free energy are as distorted, as it is with AMBER force field. However, the distortion may easily be corrected by tuning parameters of the metal – functional group interaction. This paves the way to correct available potential models in order to study metal binding to various ligands and materials.

Theory

The simulations were performed using GROMACS 2024.3 software package. [13] Standard conditions (temperature 25°C, pressure 1 bar), three-dimensional periodic boundary conditions, and a time step of 2 fs were specified. Electrostatic interactions were calculated using the Ewald particle mesh method, and van der Waals interactions were truncated at a distance of 1 nm. The simulation cells had a cubic shape (size 3×3×3 nm^3), contained a ligand with a functional group, a metal cation, and water molecules. Five functional groups that have a negative charge or contain highly electronegative atoms were studied: COO^-, NH_2, $CONH_2$, S^-, and the imidazole ring Im, Table 1. The free valence of each group was occupied by a methyl group CH_3. The protonated thiol group SH is electroneutral and contains an S atom with a moderate negative charge and electronegativity, so it was not studied.

In the initial configuration, the metal cation was positioned near the most electronegative atoms of the group. Fig. 1 shows the location of various ligands near the cation after energy minimization using the example of the Pb^{2+} ion.

Table 1. Simulated functional groups and ligands

functional group	simulated ligand	corresponding amino acids
carboxylate COO^-	acetate anion CH_3COO^-	glutamic and aspartic acids
thiolate S^-	methylthiolate anion CH_3S^-	cysteine
amino NH_2	methylamine CH_3NH_2	lysine, arginine
amide $CONH_2$	acetamide CH_3CONH_2	glutamine, asparagine
imidazole Im	4-methylimidazole $CH_3C_3N_2H_3$	histidine

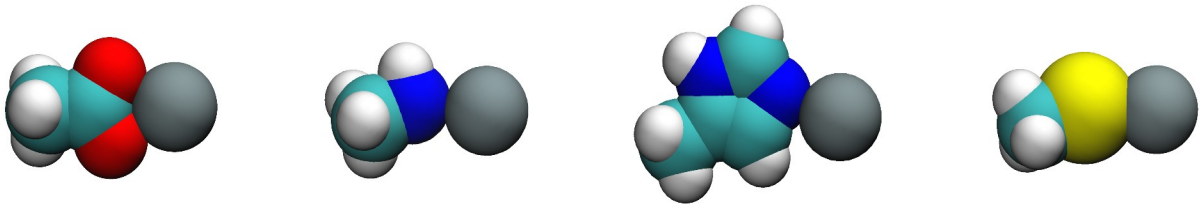

Figure 1. Placement of a Pb^{2+} ion and ligands in initial configurations for simulations. Acetamide was placed similarly to acetate ion.

Several cations were examined, with potential models of different origin. On one hand, it is the models employed in recent studies of metal binding: Cu^{2+}, Co^{2+}, Zn^{2+}, Cd^{2+}, Hg^{2+}, Pb^{2+}. [7–12] On the other hand, it is the models already available in the force field distribution: Fe^{2+}, Cu^{2+}, Sr^{2+}, Ba^{2+}, Ca^{2+}, Mg^{2+}. While calcium and magnesium are not heavy metals, the respective cations are common compo-

nents of natural and industrial waters, so were embraced by the present study, as well. Water was described by the TIP3P potential model since it was targeted during the cations' parameterization. The ligands were described by parameters taken from the OPLS-AA force field. The atomic types and point charge values of the atoms of the functional groups corresponded to their values in amino acids. The only exception was thiolate S^-, where improved Lennard-Jones parameters for S atom were used. [14]

Energy minimization was performed for the initial configuration. After that, simulations of the binding process were carried out for each cation–ligand pair. Using the thermodynamic cycle, ΔG of the studied process was represented as the negative sum of the ΔG of two stages, Eq. 1:

1) disappearance of the ion M bound to the ligand L from the solution;

2) appearance of the ion M in water (i.e., its hydration).

$$\begin{aligned} &\mathrm{ML\ (aq)} \rightarrow \mathrm{M\ (g)} + \mathrm{L\ (aq)}, && \Delta G_1 \\ &\mathrm{M\ (g)} + \mathrm{aq} \rightarrow \mathrm{M\ (aq)}, && \Delta G_2 \\ &\text{---} \\ &\mathrm{M\ (aq)} + \mathrm{L\ (aq)} \rightarrow \mathrm{ML\ (aq)}, && \Delta G_{bind} = -(\Delta G_1 + \Delta G_2) \end{aligned} \quad (1)$$

Thus, at the first stage, the initial state of the system contained a ligand and an ion interacting with the environment, and the final state contained the ligand and the ion that does not interact with the rest of the particles. At the second stage, the initial state contains water and an ion that does not interact with it, and the final state contains water and the ion hydrated.

For the calculations of ΔG at each stage, the alchemical transformation method was used, in which, in addition to the final states, intermediate states are also considered. They do not have physical counterparts (hence the term "alchemical"), but their consideration reduces the error in determining ΔG. The intensity of interactions between the ion and the environment is determined by the coupling parameter λ, which ranges from 0 (original intensity) to 1 (fully turned off) through intermediate values (corresponding to a weakened interaction). Twelve intermediate states were considered for both stages. In general, states with the following values of the parameter λ were modeled: (0, 0); (0, 0.1); (0, 0.2); (0, 0.3); (0, 0.4); (0, 0.5); (0, 0.6); (0, 0.7); (0, 0.8); (0, 0.9); (0, 1); (0.4, 1); (0.8, 1); (1, 1), where the first number is the value of λ for van der Waals interactions of the ion with the environment and the second is for electrostatic ones. In each state, the system was simulated for 4 ns under standard conditions (temperature 25°C, pressure 1 bar). The actual calculation of ΔG was performed using the Bennett acceptance ratio method as implemented in the gmx bar program. The trajectory interval of 0–2 ns was discarded as equilibration of the system.

In states with sufficiently weakened interactions the cation is no more forced to stay near the functional group and freely moves in the simulation cell. This is observed in cases of non-weakened interactions, as well, if binding between the two species is energetically not favorable. As it is not known beforehand, which simulations would exhibit dissociation of the complex, both species were restrained at their initial positions at all values of λ. The ligand was restrained by harmonic potential with a force constant of 500 kJ/(mol·nm), while for the cation, a flat-bottom restraint was chosen, as it affects the system's dynamics to lesser extent than a standard harmonic restraint. There, no force was exerted on the cation when it stayed within 0.1 nm of its initial position. Beyond this range, a harmonic potential with a force constant of 500 kJ/(mol·nm) was applied to the cation. Its magnitude was calculated for metal – ligand distance reduced by 0.1 nm in order to make the potential energy a continuous function of the distance.

Results and Discussion

The immediate results of alchemical free energy simulations obtained with the considered set of potential models are collected in Table 2.

Table 2. Calculated alchemical free energies (kJ/mol)

cation	$-\Delta G_2$	ΔG_1				
		COO^-	S^-	NH_2	$CONH_2$	Im
external parameters						
Cu^{2+}	1755.9 ± 0.5	1800.2 ± 0.7	1785.4 ± 0.3	1755.6 ± 0.2	1740.2 ± 0.5	1732.6 ± 0.3
Co^{2+}	1679.4 ± 0.2	1717.2 ± 1.3	1712.5 ± 1.0	1679.3 ± 0.3	1665.3 ± 0.2	1655.9 ± 0.6
Cd^{2+}	1680.1 ± 0.3	1717.1 ± 0.8	1714.5 ± 0.3	1680.4 ± 0.4	1663.5 ± 0.5	1658.4 ± 0.6
Zn^{2+}	1732.2 ± 0.4	1770.2 ± 0.7	1761.6 ± 1.0	1732.1 ± 0.3	1717.0 ± 0.6	1708.5 ± 1.0
Pb^{2+}	1349.0 ± 0.3	1362.6 ± 0.8	1353.7 ± 0.4	1348.3 ± 0.5	1346.2 ± 0.1	1345.7 ± 0.7
Hg^{2+}	1669.2 ± 0.2	1704.4 ± 1.1	1703.4 ± 0.4	1669.2 ± 0.4	1657.1 ± 0.7	1641.4 ± 0.7
built-in parameters						
Cu^{2+}	1572.0 ± 0.5	1610.7 ± 0.4	1595.4 ± 0.4	1571.7 ± 0.3	1567.5 ± 0.6	1567.7 ± 1.0
Fe^{2+}	1659.9 ± 0.2	1695.5 ± 0.7	1694.0 ± 0.5	1659.2 ± 0.5	1643.7 ± 0.4	1644.3 ± 1.2
Mg^{2+}	1817.3 ± 0.3	1853.4 ± 0.7	1842.0 ± 0.2	1816.6 ± 0.5	1815.5 ± 0.7	1792.8 ± 0.8
Ca^{2+}	1495.2 ± 0.4	1520.9 ± 0.4	1509.1 ± 0.5	1494.4 ± 1.1	1491.7 ± 0.2	1490.4 ± 0.5
Sr^{2+}	1347.6 ± 0.4	1359.3 ± 0.4	1353.0 ± 0.2	1345.8 ± 0.5	1343.3 ± 0.3	1340.8 ± 0.6
Ba^{2+}	1215.1 ± 0.4	1220.7 ± 0.6	1218.7 ± 0.5	1215.3 ± 0.5	1212.6 ± 0.3	1211.5 ± 0.2

The final obtained ΔG_{bind} values are collected in Table 3 and represented visually in Fig. 2.

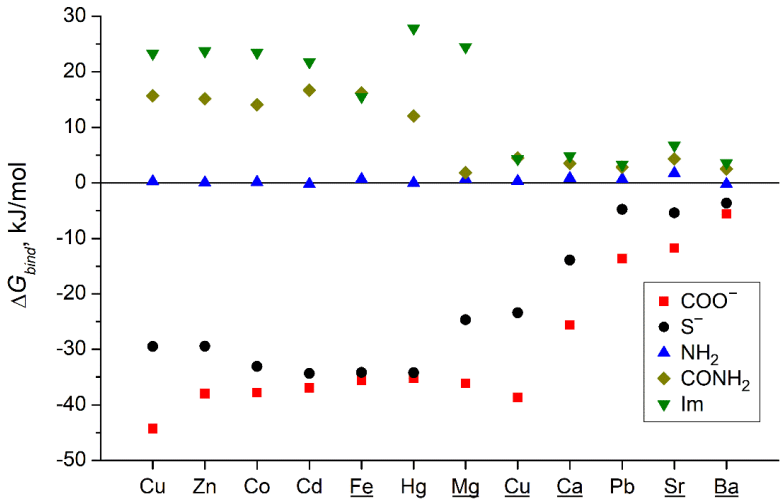

Figure 2. Binding free energies of a series of divalent cations to various functional groups. The cations described with built-in potential models are underlined.

According to the simulation results, metal cations interact most strongly with deprotonated carboxyl group COO^-, which is probably provided by its negative charge. Highly intense interaction is observed for transition metals and Mg^{2+} (ΔG_{bind} of ≈ -40 kJ/mol), while for alkaline earth metals and Pb^{2+} the interaction is much weaker (ΔG_{bind} of -26 to -6 kJ/mol).

The interaction energy of cations with thiol group S^- generally follows the trend of COO^- group. For most metals, ΔG_{bind} is 10–15 kJ/mol lesser than that with COO^- group, while for Co^{2+}, Cd^{2+}, Hg^{2+}, Fe^{2+}, and Ba^{2+} the two are very close.

Interaction of metal cations with all other groups is found energetically unfavorable with ΔG_{bind} ranging from 0–5 kJ/mol for NH_2 and SH groups to >10 kJ/mol for amide group $CONH_2$ and imidazole ring Im when bound to transition metals. This means it is energetically more favorable for the metal cation to have a complete hydration shell and stay in bulk solution than to replace one or several water molecules with these functional groups.

Table 3. Calculated ΔG_{bind} of divalent cations with ligands containing amino acid functional groups (kJ/mol)

cation	ΔG_{bind}				
	COO^-	S^-	NH_2	$CONH_2$	Im
external parameters					
Cu^{2+}	-44.3	-29.5	0.3	15.7	23.3
Co^{2+}	-37.8	-33.1	0.1	14.1	23.3
Cd^{2+}	-37.0	-34.4	-0.2	16.7	13.8
Zn^{2+}	-38.0	-29.4	0.1	15.2	23.7
Pb^{2+}	-13.6	-4.8	0.7	2.8	3.3
Hg^{2+}	-35.2	-34.2	0.0	12.1	19.9
built-in parameters					
Cu^{2+}	-38.7	-23.4	0.3	4.5	3.2
Fe^{2+}	-35.6	-34.2	0.7	16.2	15.1
Mg^{2+}	-36.1	-24.7	0.7	1.8	22.1
Ca^{2+}	-25.6	-13.9	0.9	3.5	4.5
Sr^{2+}	-11.8	-5.4	1.8	4.3	4.9
Ba^{2+}	-5.6	-3.6	-0.2	2.5	2.8

In laboratory practice, the process of binding of a metal ion to a compound in 1:1 stoichiometry is quantitatively described by the first stability constant of the complex β_1, Eq. 2. Numerous values of β_1 are available in the literature, so the obtained values of ΔG_{bind} can be compared with the experimental data to check their correctness. In several cases, the comparison had to be made with some structurally similar ligand, provided the binding occurs through the same functional group. The corresponding data are given in Table 4.

$$M\,(aq) + L\,(aq) \rightleftarrows ML\,(aq), \quad \beta_1, \ \Delta G_{bind} = -RT \ln \beta_1 \tag{2}$$

Table 4. Comparison of experimental and calculated binding free energies (kJ/mol)

cation	experimentally examined ligand	lg β_1	$\Delta G_{bind\ exp}$	$\Delta G_{bind\ calc}$
ligand CH_3COO^-				
Cu^{2+}	CH_3COO^-	1.7 – 2.66 [15,16]	-9.7 – -15.17	-44.3 (external) -38.7 (built-in)
Zn^{2+}	CH_3COO^-	-0.15 – 1.04 [16]	-0.86 – -5.94	-38.0
Cd^{2+}	CH_3COO^-	0.74 – 1.38 [16]	4.22 – -7.88	-37.0
Pb^{2+}	CH_3COO^-	2.2 [15]	-12.6	-13.6
Hg^{2+}	CH_3COO^-	4.65 – 5.89 [16]	-26.55 – -33.62	-35.2
Ca^{2+}	CH_3COO^-	0.45 [15]	-2.57	-25.6
Mg^{2+}	CH_3COO^-	0.47 [16]	-2.68	-36.1
ligand CH_3S^-				
Cd^{2+}	cysteine anion	10.3 [17]	-58.8	-34.4
Hg^{2+}	cysteine anion	14.2 – 37.8 [17]	-81.1 – -215.8	-34.2
Pb^{2+}	cysteine anion	13.16 [16] 13.85 [17]	-75.13 -79.07	-4.8
ligand CH_3NH_2				
Cu^{2+}	CH_3NH_2	4.11 [18]	-23.47	0.3 (external) 0.3 (built-in)
Co^{2+}	$C_3H_7NH_2$	2.12 [16]	-12.10	0.1
Zn^{2+}	$C_2H_5NH_2$	2.30 [16]	-13.13	0.1
Cd^{2+}	CH_3NH_2	2.75 [18]	-15.70	-0.2
Hg^{2+}	CH_3NH_2	8.7 [18]	-49.7	0.0
ligand CH_3CONH_2				
Ca^{2+}	H_2NCONH_2	-0.28 [16]	1.60	3.5
Mg^{2+}	H_2NCONH_2	-0.31 [16]	1.77	1.8

ligand Im				
Cu^{2+}	4-methylimidazole 1-methylimidazole imidazole	4.13 [19] 4.22 [19] 4.2 – 4.6 [16,19]	-23.58 -24.09 -24.0 – -26.3	24.9 (external) 3.2 (built-in)
Co^{2+}	imidazole	2.23 – 2.43 [16]	-12.73 – -13.87	23.3
Zn^{2+}	imidazole	2.60 [16]	-14.84	24.1
Cd^{2+}	imidazole	2.66 – 2.71 [16]	-15.19 – -15.47	13.8

It can be seen that in the case of the COO^- group, the discrepancy is multifold towards overestimation and reaches tens of kJ/mol, a notable exception being Hg^{2+} cation. This indicates a systematic error in reproducing the balance of interactions in these solutions. Its cause cannot be explained only by the high intensity of interactions with negative charged ligand, since the results for another anionic group (S^-) exhibit discrepancy of the opposite character (towards underestimation). This effect regarding the interaction with acetate ion was previously discovered for other metals and potential models. To correct it, reducing the charge of the cation and/or the ligand it has been suggested. [20] Here it is shown that the studied potential models are affected, as well. The amide group binds very weakly to metal cations in both the experiment and the simulation.

Oppositely, binding free energy with thiolate group S^- is severely underestimated. The discrepancy may be partly caused by the difference in structure and binding mode between cysteine anion and simulated CH_3S^- anion. However, for the compared cations, coordination through S^- is the most important contribution, which justifies the comparison. [21–23]

On the other hand, no binding was predicted between the metals and amino group, which is not true. For the case of imidazole and its derivatives, the simulations demonstrate strong energetic disadvantage of binding, although the experimental data indicate the formation of moderately stable complexes. The trend is consistent for all metals. Further, previously it was shown that computed ΔG_{bind} value does not significantly depend on the initial configuration of the simulated complex. [6] Hence, the imidazole model is likely the reason of the discrepancy.

Summarizing, it is seen that regardless the chosen force field, available models of metal cations struggle to correctly reproduce binding free energies to important functional groups. Previously, it was shown that the error persists in complexes with coordination number 2, as well. [6] This hinders computational studies of metal binding to a variety of ligands and severely limits application of molecular dynamics in research of water treatment, complexation etc. Therefore, it is of interest to discuss the possible remedies to this problem. For thiolate group, incorporation of electronic polarizability was shown to improve the accuracy of binding energies to Cu^+ and H^+. [14] However, fixed-charge force fields are still a prevalent choice in the literature, so it is reasonable to focus on them here.

At given conditions, provided correct simulation setup, the results of a classical MD simulation are determined by the totality of interaction parameters between atoms in the system. Conventionally, the parameters are calculated on the basis of parameters, assigned to each of interacting atoms; the latter usually are fixed electric charge and characteristics of the Lennard–Jones potential σ and ε. In particular, in OPLS-AA force field, the van der Waals interaction between two atoms i and j is computed using the so-called geometric combination rule, Eq. 3

$$U_{LJ,ij} = 4\varepsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right]$$
$$\sigma_{ij} = \sqrt{\sigma_i \cdot \sigma_j} \qquad (3)$$
$$\varepsilon_{ij} = \sqrt{\varepsilon_i \cdot \varepsilon_j}$$

Using validated potential models prohibits tweaking individual parameters of atoms because this would break the models' validation. However, in principle, one is free to adjust the parameters of interactions of pairs of atoms by overriding the combination rule. Here this approach is explored for several metal – ligand pairs and found to be rather effective, Table 5. For each considered system, the ad-

justment was done in iterative way. The interaction between the cation and the donor atoms of the ligand was tuned, and its initial values of σ_{ij} and ε_{ij} were found using the combination rule (Eq. 3). Several (2-3) options with somewhat reduced or increased σ_{ij} (by less than ±0.1 nm) were simulated, and the effect of the adjustments on $\Delta G_{bind\ calc}$ guided the choice of the next σ_{ij} values to try. For the case of Cu^{2+} with 4-methyl-imidazole, tweaking of ε_{ij} in addition to σ_{ij} appeared necessary. In each case, no more than 6 trials were enough to get the final parameters.

Table 5. Refined parameters for some cation – ligand interactions

cation	ligand	interaction	σ_{ij}, nm	ε_{ij}, kJ/mol	$\Delta G_{bind\ exp}$, kJ/mol	$\Delta G_{bind\ calc}$, kJ/mol
Cu^{2+}	CH_3COO^-	Cu^{2+} – O (both atoms)	0.2484 → 0.263	2.0472 (no change)	-9.7 – -15.17	-11.7
Cu^{2+}	CH_3NH_2	Cu^{2+} – N	0.2603 → 0.236	1.8419 (no change)	-23.43	-26.8
Cu^{2+}	4-methyl-imidazole	Cu^{2+} – N (both atoms)	0.2603 → 0.22	1.8419 → 40	-23.55	-22.3
Pb^{2+}	CH_3S^-	Pb^{2+} – S	0.3674 → 0.32	0.2297 (no change)	-78.96*	-79.6

* corresponds to cysteine anion.

Importantly, this approach is safe and does not affect the performance of the individual cation and ligand potential models. The corrected parameters may be employed in simulations of cations' binding to various materials functionalized with these groups.

Conclusions

Using classical molecular dynamics simulation, the free energy change ΔG_{bind} upon binding of a series of divalent metal cations to a set of functional groups present in natural amino acids was evaluated using OPLS-AA force field. Despite the fact that the applied potential models are validated and commonly used, the ΔG_{bind} values generally do not correspond well to the experimental data regarding the stability constants of the complexes. The most reasonable reproduction was observed for thiolate group S^-, but the ΔG_{bind} values were systematically underestimated. On the contrary, the calculated binding energies with carboxylate group were extremely overestimated. Binding with amino group and imidazole was found to be energetically unfavorable, although experimental data indicate formation of complexes. Thus, the obtained data emphasizes the need for careful application of molecular dynamics modeling with OPLS-AA force field for quantitative estimation of binding energy of metal cations to proteins and similar materials. Successful prediction of ΔG_{bind} requires careful selection of the force field or correcting existing potential models.

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Conflict of Interest: The author declares no conflict of interest.

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В. С. Фарафонов. Вільні енергії зв'язування двозарядних катіонів із функціональними групами амінокислот у силовому полі OPLS-AA.

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Очистка води від іонів важких металів являє собою нагальну екологічну потребу. Активно досліджуються методи зв'язування іонів металів за допомогою природних матеріалів, таких як рослинні білки, а також штучних матеріалів, наприклад функціоналізованих алотропних модифікацій Карбону. Карбоксильні, тіольні, аміногрупи здатні до комплексоутворення з катіонами металів, що призводить до видалення забруднень із води. Методи обчислювальної хімії, включно з класичним молекулярно-динамічним моделюванням, активно застосовуються під час пошуку придатних матеріалів. У статті перевірена правильність відтворення вільних енергій зв'язування ряду двозарядних катіонів металів із функціональними групами, наявними в амінокислотах, із використанням силового поля OPLS-AA. Розглянуті як стандартні вбудовані, так і сучасно застосовані потенціальні моделі. Проведене порівняння з експериментально виміряними константами стійкості модельованих комплексів або їхніх структурних аналогів. Розрахунки вільних енергій виконані методом алхімічного перетворення. Показано, що незважаючи на валідність потенціальних моделей, вільні енергії зв'язування з функціональними групами амінокислот загалом відтворюються погано: сильно перебільшені для карбоксильної групи, занижені для тіолатної та аміногрупи, некоректні для імідазолу. Це вказує, що силове поле OPLS-AA слід застосовувати з обережністю для розрахунку енергетичних характеристик зв'язування металів. Показаний спосіб виправити потенціальні моделі для точного відтворення експериментальних значень, він застосований до чотирьох комплексів катіон – ліганд.

Ключові слова: *вільна енергія, молекулярно-динамічне моделювання, макромолекула білка, важкі метали, константа стійкості комплексу.*

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