JCRS

Journal of Chemical Reactivity and Synthesis 2024: 14(1) 18-30

Research Article

Comparative Analysis of Histidine-14 Reactivity in C-terminal truncated beta-amyloid peptide in the Presence of Copper and Zinc Ions: Insights from Molecular Dynamics Simulations and Density Functional Theory

Diba Aslani Firozabadi[1], Mohammad Reza Bozorgmehr[1,*], S. Ali Beyramabadi[1] , Sharareh Mohseni[2]

[1]Department of Chemistry, Mashhad Branch, Islamic Azad University, Mashhad, Iran

[2]Department of Chemistry, Quchan Branch, Islamic Azad University, Quchan, Iran

ARTICLE INFO:

Received:
19 July 2024

Accepted:
11 September 2024

Available online:
20 September 2024

✉: M.R. Bozorgmehr
bozorgmehr@mshdiau.ac.ir

ABSTRACT

This study investigates the reactivity of the beta-amyloid peptide, particularly focusing on its interactions with copper and zinc ions, which are relevant to the progression of Alzheimer's disease. Molecular dynamics simulations were performed to explore the effects of copper and zinc ions on the stability and binding affinity of the peptide. The presence of copper ions was found to decrease the relative stability of peptide. Conformational analysis revealed that copper ions preferentially bind to the N-terminal residues, with a particularly high affinity for His14. The addition of zinc ions reduced the overall binding affinity of copper ions to the peptide but did not significantly alter the strong interaction with His14. Density functional theory (DFT) calculations on the sampled peptide structures provided quantum descriptors, including the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) energies, which are indicative of reactivity. The results suggest a significant decrease in the reactivity of His14 in the presence of copper ions, with a further reduction observed in the combined presence of both copper and zinc ions. These findings contribute to understanding the molecular mechanisms underlying metal ion-induced conformational changes in beta-amyloid peptides and their role in Alzheimer's disease.

Keywords: Alzheimer; metal; reactivity; beta amyloid; aggregation.

1. Introduction

Alzheimer's disease (AD) is a neurological disorder marked by the abnormal self-assembly of beta-amyloid (Aβ) peptide into toxic oligomers and fibrils, originating from the beta-amyloid precursor protein [1]. While the exact mechanisms of Aβ processing and aggregation are not fully understood, the disease is significantly influenced by transition metal ions and oxidative metabolism, which contribute to oxidative stress in specific brain regions. Irregularities in the brain's transition metal metabolism, particularly involving copper, iron, and zinc, are linked to increased oxidative damage and play a critical role in the formation and toxicity of Aβ fibrils. These metals interact with Aβ, altering its structure and promoting plaque formation, but the complexity of these interactions poses challenges for traditional experimental studies [2].

The most abundant beta-amyloid involved in the formation of amyloid plaques in Alzheimer's disease is the 40-residue beta-amyloid (Aβ1-40). However, shorter beta-amyloids, such as Aβ1-26 , Aβ1-30, and Aβ1-36, also contribute to fibril formation. The amino acid sequence of the Aβ1-40 peptide is DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVV, with a hydrophobic C-terminal region. The interaction of beta-amyloid peptides with other species is primarily driven by hydrophobic forces. Studying the interactions of C-terminal truncated beta-amyloid peptides (Aβ1-26, Aβ1-30, Aβ1-36) with ions can provide insights into the mechanisms underlying Alzheimer's disease. Among the amino acid residues within these peptides, histidine residues, especially histidine-14 (His14), are of particular interest due to their ability to bind metal ions such as copper (Cu^{2+}) and zinc (Zn^{2+}). The interaction between His14 and metal ions has been implicated in the aggregation and toxicity of beta-amyloid peptides. Despite its importance, the precise molecular mechanisms underlying these interactions remain unclear[3,4].

This study aims to elucidate the reactivity of His14 in C-terminal truncated beta amyloid peptide, Aβ1-26, in the presence of Cu^{2+} and Zn^{2+} ions, using a combination of molecular dynamics (MD) simulations and density functional theory (DFT). The study further explores the impact of peptide truncation on His14 reactivity to provide a deeper understanding of metal ion interactions.

2. Method

The three-dimensional structure of the beta-amyloid peptide was sourced from the protein data bank with the code 1Z0Q [5]. This structure contains 30 modes, with the third mode used as a basis for designing other structures. From this peptide, Aβ1-26 variant were developed. Three simulation boxes were created, each with a truncated beta-amyloid peptide, Aβ1-26, positioned at the center. Following the model proposed in reference [6], three copper ions (Cu II) were introduced into two of the three simulation boxes to achieve a 1:3 ratio of peptide to copper ions. Additionally, as outlined in Table 1, three zinc ions (Zn) were added to the simulation boxes.

Table 1. Designed simulation systems along with their components

System number	Number of $A\beta 1-26$	Cu^{2+}	Zn^{2+}
I	1	0	0
II	1	3	0
III	1	3	3

The truncated peptide structure was derived from the full-length peptide using PyMol software [7]. The simulation boxes were designed with dimensions extending one nanometer from the peptide surface, adhering to the cutoff distance. Each box was then filled with SPC-model water [8], and chlorine counterions were added to neutralize the system's total charge.

Temperature (300 K) and pressure (1 bar) were maintained using the Berendsen weak coupling thermostat [9]. Van der Waals interactions were managed with a 1.4 nm cutoff, and electrostatic interactions were calculated using the Particle Mesh Ewald method. The LINCS algorithm [10] was applied to constrain peptide bond lengths, while the SETTLE algorithm [11] was used to maintain water geometry. Energy minimization was performed both before and after the addition of chlorine ions and SPC water molecules to ensure that the maximum force on any atom remained below 1000 kJ/mol. To allow for the relaxation of water molecules around the peptides, position restraints with a force constant of 1000 kJ/mol were applied. Finally, molecular dynamics simulations were conducted for 100 ns with a 2 fs time step. Each simulation was repeated three times under different initial conditions to reduce dependency on initial setups and enhance accuracy. The force field parameters for metal ions were consistent with those in reference [6]. All calculations were performed using GROMACS software version 5.1.2 [12].

3. Results and Discussion

In order to check the relative stability of C-terminal truncated beta-amyloid peptide in the designed systems, the quantity of RMSD (root-mean-square-deviation) was calculated. The RMSD value of α-carbon (Cα-RMSD) in Aβ1-26 was obtained using the following equation:

$$RMSD(t_1,t_2)=\left[\frac{1}{M}\sum_{i=1}^{N}m_i\left\|r_i(t_1)-r_i(t_2)\right\|\right]^{\frac{1}{2}} \qquad (1)$$

Where r_i is the atomic position at time t and $M=\sum_{i=1}^{N}m_i$ .The results obtained for the designed systems are shown in Fig.1.

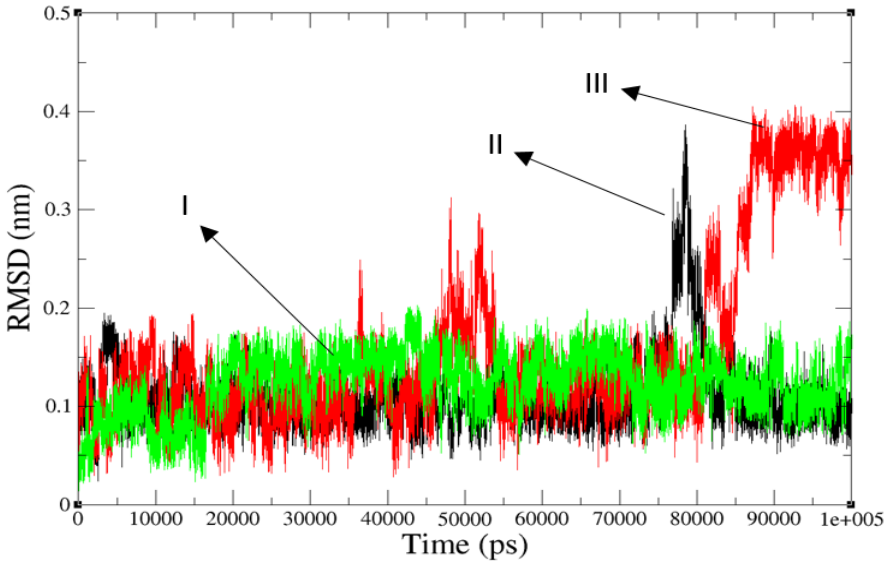

Fig. 1. Cα-RMSD values (nm) versus time (ps) for simulated systems

According to Figure 1, it can be seen that the presence of copper ion decreased the relative stability of Aβ1-26. This decrease in relative stability is exacerbated by the presence of zinc ions. In order to control the simulation parameters and compare with the experimental results, conformation factor (CF) were calculated for each peptide residue. The conformational parameter is a measure of the binding affinity of peptide residues to ions. Based on method developed by Housaindokht et al. [13] the CF was determined as follows:

The number of ion-peptide collisions for each Aβ1-26 residue was counted throughout the simulation, and the total collisions for each residue and across all residues were determined. The overall collisions were averaged by dividing by 26, the total number of peptide residues. The average was then divided by the number of collisions for each residue to calculate the conformation factor (CF), with a CF greater than 1 indicating a higher binding affinity of the sequence for the ion.The calculated values for quantity CF in the designed systems are listed in Table 2.

Table 2. P_i values calculated for peptide residues in the studied systems

Res#	system		
	I	II	III
1	---	4.0	2.8
2	---	6.2	5.1
3	---	4.2	3.9
4	---	2.1	1.8
5	---	1.8	1.6
6	---	3.8	2.9
7	---	3.9	2.7
8	---	5.5	4.1
9	---	6.6	5.5
10	---	8.0	7.3
11	---	11.6	10.3
12	---	11.6	11.1
13	---	15.7	14.4
14	---	19.6	18.6
15	---	15.8	15.1
16	---	12.7	11.5
17	---	10.3	9.5
18	---	6.5	5.2
19	---	2.5	1.5
20	---	0.6	0.5
21	---	0.8	0.7
22	---	0.9	0.7
23	---	1.1	0.9
24	---	1.9	1.7
25	---	3.0	2.7
26	---	4.8	3.7

According to the values reported in Table 2, it can be seen that the binding affinity of N-terminal residues to copper ion is higher than the binding affinity of C-terminal residues. Also, it can be seen that the binding affinity of copper ion to His14 is high. The presence of zinc ion has caused a relative decrease in the affinity of copper ion to bind to peptide residues. However, in the presence of zinc ion, the binding affinity of copper ion to His14 is high. These observations are in good agreement with experimental observations and previous calculations [14-16]. In order to perform DFT calculations, samples must be taken from the performed simulations. The Free Energy Landscape (FEL) method was employed for sampling [17]. FEL provides insights into the conformational space of a peptide by exploring states similar to its native structure. To construct a three-dimensional FEL, the probability of the system being in a specific state—characterized by a particular value of q_α for variables of interest, such as the radius of gyration and $C_\alpha - RMSD$ is considered proportional to $e^{\frac{G_\alpha}{kT}}$, where G_α represents the free energy of that state. This probability distribution is then used to derive the FEL.

$$G_\alpha = -kTln\left[\frac{P(q_\alpha)}{P_{max}(q)}\right] \quad (2)$$

The Gibbs free energy diagram was generated using Equation 1, where k represents the Boltzmann constant, T is the simulation temperature, $P(q_\alpha)$ is the estimated probability density function derived from a histogram of the MD data, and $P_{max}(q)$is the probability of the most probable state. The structure of the sampled peptide along with the corresponding free energy diagram was obtained from the simulations. The result is shown in figures 2 to 4.

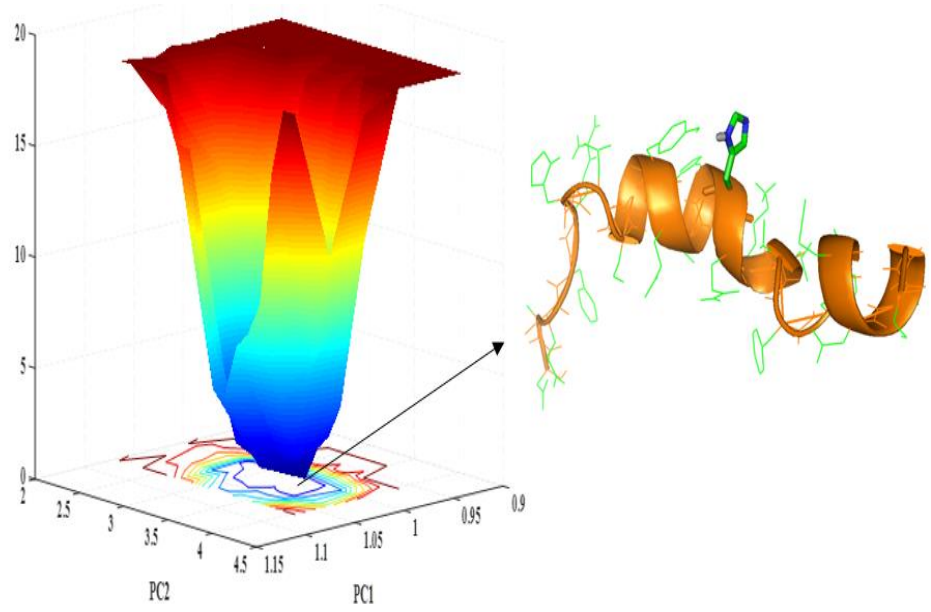

Fig. 2. FEL between PC1 (RMSD) and PC2 (Rg) for the $A\beta 1-26$ in system I.

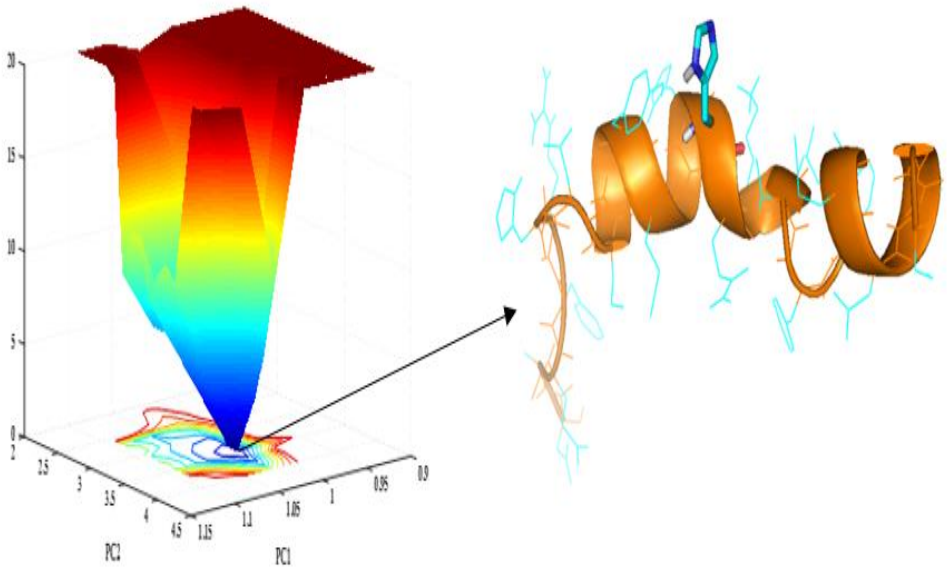

Fig. 3. FEL between PC1(RMSD) and PC2 (Rg) for the $A\beta 1-26$ in system II.

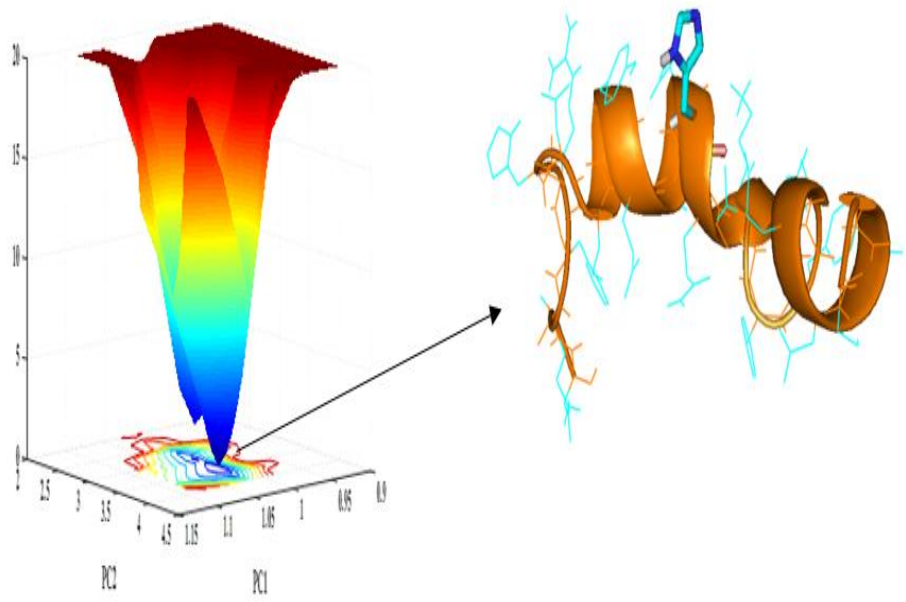

Fig. 4. FEL between PC1 (RMSD) and PC2 (Rg) for the $A\beta 1-26$ in system III.

According to these figures, it can be seen that the presence of copper and zinc ions has reduced the distribution of structures with the lowest Gibbs free energy. Likewise, in these figures, it is observed that the structure of the peptide has changed in the presence of ions. The position of His14 shown as stick representation in these three figures. Beta-amyloid peptide structures sampled from molecular dynamics simulations were used for density functional theory calculations. For this purpose, three different layers were defined in the sampled peptide structure. The residue of His14 is located in the first layer, which is considered the high layer. In the second layer or the medium layer, two residues around His14 are included. Other peptide residues were considered as low layer (Fig. 5).

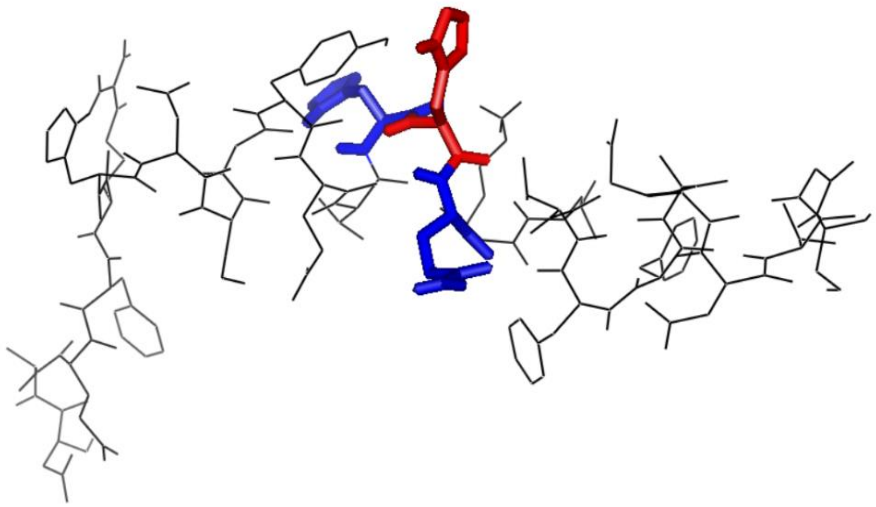

Fig. 5. different layers considered for quantum calculations. Black(low layer), blue (medium layer) and red(high layer)

In the lower, medium, and high layer, molecular mechanics, Hartree-Fock calculations with 3-21G basis function and B3LYP with 6-31G basis function were performed, respectively. The values of quantum descriptors the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) and accordingly the difference between these two quantities, which is a measure of reactivity, were calculated. The results are listed in Table 3.

Table 3. The calculated chemical reactivity descriptor of His14 residue in studied systems at B3LYP/6–31G levels of theory (kcal/mol)

system	E_{HOMO}	E_{LUMO}	E_{gap}
I	-221.66	-145.80	75.86
II	-231.75	-151.17	80.58
III	-232.71	-151.11	81.60

The obtained results show that the reactivity of histidine 14 decreases in the presence of copper ions. This reduction in the reactivity of histidine 14 is reduced in the binary system of copper and zinc ions.

4. Conclusion

This study provides significant insights into the interactions between the truncated beta-amyloid peptide Aβ1-26 and metal ions, particularly copper and zinc, which are implicated in the pathogenesis of Alzheimer's disease. Through molecular dynamics simulations, we observed that the presence of copper ions destabilizes the peptide structure, a phenomenon that is further amplified by the introduction of zinc ions. The analysis of conformational factors revealed a strong binding affinity of copper ions to the N-terminal residues, with His14 being particularly reactive. Interestingly, while zinc ions reduced the overall binding affinity of copper to the peptide, they did not significantly diminish the interaction with His14. Free energy landscape analysis indicated that these metal ions induce conformational changes, reducing the population of structures with the lowest Gibbs free energy. This suggests a shift in the peptide’s conformational equilibrium due to metal ion binding. Moreover, density functional theory calculations highlighted a decrease in the reactivity of His14 in the presence of copper ions, with an even greater reduction observed in the combined presence of copper and zinc ions. These findings underscore the complex role of metal ions in modulating the structure and reactivity of beta-amyloid peptides, offering deeper understanding of their contribution to the molecular mechanisms driving Alzheimer's disease.

References:

[1] Rogers, J., Cooper, N.R., Webster, S., Schultz, J., McGeer, P.L., Styren, S.D., Civin, W.H., Brachova, L., Bradt, B. and Ward, P. (1992) *Proceedings of the National Academy of Sciences*, **89**, 10016.

[2] Mantyh, P.W., Ghilardi, J.R., Rogers, S., DeMaster, E., Allen, C.J., Stimson, E.R. and Maggio, J.E. (1993) *Journal of neurochemistry*, **61**, 1171.

[3] Firozabadi, D.A., Bozorgmehr, M.R., Beyramabadi, S.A. and Mohseni, S. (2023) *Current Proteomics*, **20**, 145.

[4] Bush, A.I., Pettingell Jr, W.H., Paradis, M. and Tanzi, R.E. (1994) *Journal of Biological Chemistry*, **269**, 12152.

[5] Crescenzi, O., Tomaselli, S., Guerrini, R., Salvadori, S., D'Ursi, A.M., Temussi, P.A. and Picone, D. (2002) *European journal of biochemistry*, **269**, 5642.

[6] Turner, M., Mutter, S.T. and Platts, J.A. (2019) *Journal of Biomolecular Structure and Dynamics*, **37**, 4590.

[7] DeLano, W.L. (2004) *Delano Scientific: San Carlos, CA, USA*, 1.

[8] Zielkiewicz, J. (2005) *The Journal of chemical physics*, **123**.

[9] Lemak, A. and Balabaev, N. (1994) *Molecular Simulation*, **13**, 177.

[10] Hess, B., Bekker, H., Berendsen, H.J. and Fraaije, J.G. (1997) *Journal of computational chemistry*, **18**, 1463.

[11] Miyamoto, S. and Kollman, P.A. (1992) *Journal of computational chemistry*, **13**, 952.

[12] Berendsen, H.J., van der Spoel, D. and van Drunen, R. (1995) *Computer physics communications*, **91**, 43.

[13] Housaindokht, M.R., Bozorgmehr, M.R. and Bahrololoom, M. (2008) *Journal of theoretical biology*, **254**, 294.

[14] Sohrabi, M., Bozorgmehr, M.R. and Momen-Heravi, M. (2024) *Journal of Biomolecular Structure and Dynamics*, 1.

[15] BORGHESANI, V., ALIES, B., SAYEN, S., GUILLON, E., FALLER, P. and HUREAU, C. (2016) *Casa Convalescència ALBA Synchrotron 7-10 June 2016 Barcelona*, 89.

[16] Hureau, C. (2012) *Coordination Chemistry Reviews*, **256**, 2164.

[17] Pietrucci, F. (2017) *Reviews in Physics*, **2**, 32.