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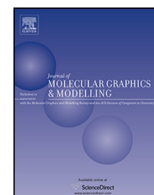

# Conformational changes of Aβ (1–42) monomers in different solvents

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ABSTRACT

Amyloid proteins are known to be the main cause of numerous degenerative and neurodegenerative diseases. In general, amyloids are misfolded from monomers and they tend to have β-strand formations. These misfolded monomers are then transformed into oligomers, fibrils, and plaques. It is important to understand the forming mechanism of amyloids in order to prevent degenerative diseases to occur. Aβ protein is a highly noticeable protein which causes Alzheimer's disease. It is reported that solvents affect the forming mechanism of Aβ amyloids. In this research, $A\beta_{1-42}$ was analyzed using an all-atom MD simulation with the consideration of effects induced by two disparate solvents: water and DMSO. As a result, two different conformation changes of $A\beta_{1-42}$ were exhibited in each solvent. It was found that salt-bridge of Asp23 and Lys28 in $A\beta_{1-42}$ was the key for amyloid folding based on the various analysis including hydrogen bond, electrostatic interaction energy and salt-bridge distance. Since this salt-bridge region plays a crucial role in initiating the misfolding of $A\beta_{1-42}$, this research may shed a light for studies related in amyloid folding and misfolding.

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## 1. Introduction

Amyloid proteins are implicated in neurodegenerative diseases, e.g., Alzheimer's, Parkinson's, Huntington's, and transmissible spongiform encephalopathy. Such neurodegenerative diseases concerned with amyloid proteins are called amyloidosis [1,2]. In these disease states, normal cell function in the cerebrum of human brain is disrupted by the deposition of amyloid proteins. For example, prion proteins, which are the source of spongiform encephalopathy, are deposited as fibrillar, plate, and plaque structures and have been visualized and characterized by experimental techniques such as cryo electron microscopy (cryo-EM) [3]. Fibrillar and plaque structures, which arouse the degenerative diseases such as type II diabetes, cardiovascular and dialysis-related diseases, are also formed by other amyloid proteins such as human islet polypeptide (hIAPP), transthyretin (TTR), and β2-microglobulin. These structures have also been characterized by experimental techniques through solid-state nuclear magnetic resonance (ss-NMR), scanning electron microscopy (SEM), and transmission electron microscopy (TEM) [4–7]. These fibrillar and plaque structures range from nano- to microscale in size, and are not easily decomposed under physiological conditions because of high structural stability [8–10].

Ranging from nano to microscale sizes, amyloid proteins in plaque and fibrillar structures are related to neuro-degenerative and degenerative diseases. However, amyloid oligomer structure is more implicated than plaque or fibrillar shapes in neuro-degenerative and degenerative diseases. Normally, oligomer structures composed of Aβ peptides were generated by β-amyloid precursor proteins due to the proteolysis [1,11,12]. These amyloid oligomers have been recognized as an important agent that can affect cell cytotoxicity and growth mechanism of fibrillar or plaque structures. Not only oligomers, but also cytotoxic characteristics of amyloid oligomer against functional cells are sources of higher-order amyloid structures like plaques and fibrils [12,13]. Specifically, oligomeric amyloid proteins and amyloid monomer structures are transformed to aggregation state by misfolding and protein-membrane mediation, which simultaneously remove the lipid layer of membranes and disrupt the normal functional cells [14–17]. Developed amyloid proteins in fibrillar shapes have been recognized as toxic agents for the normal organ cells in living bodies, however, amyloid oligomer structures have more toxic characteristics than developed amyloid protein structures. Furthermore, the role of the Aβ amyloid oligomer as seed agents of aggregated amyloid fibrils has been revealed through the experimental technique via TEM [18]. Ahmed et al., revealed the

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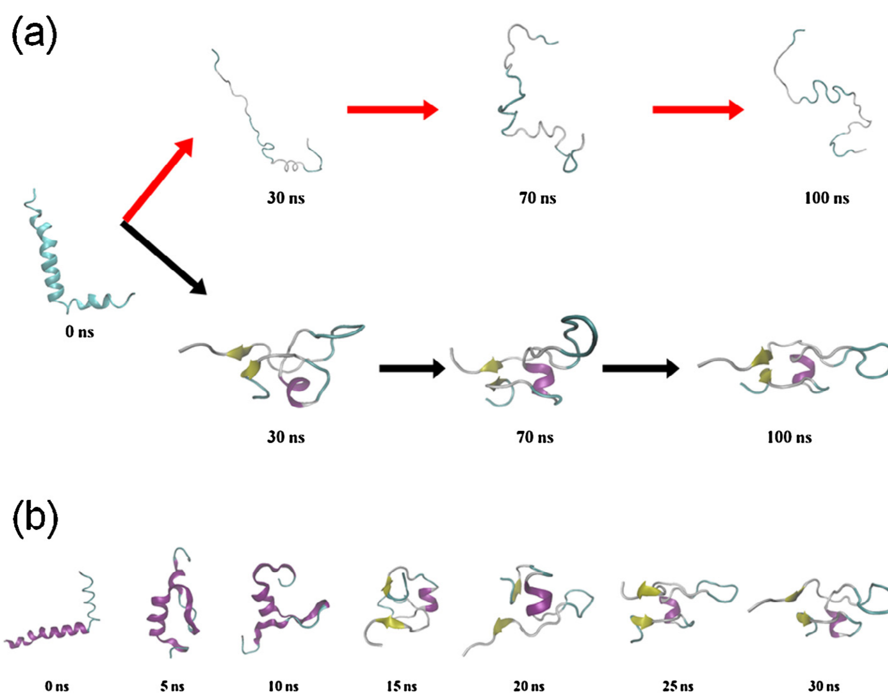


**Fig 1.** (a) Trajectory changes of Aβ monomer structure under DMSO (upper, colored in red arrow) and water solvents (lower, colored in black arrow) during 100 ns equilibrated MD simulations. (b) Trajectory variation of Aβ monomer structure under water during initial 30 ns equilibrated MD simulations.(For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

aggregation of Aβ amyloid oligomer under low salt concentration and low temperature condition, and investigated the transformation of Aβ oligomer to Aβ proto-fibril by increasing the temperature and salt concentration [18]. Also, they found out that the mature amyloid fibrils were formed after incubating the proto-fibrils with the same conditions. Also, Vivekanandan et al. reported the structures of $A\beta_{1-40}$ amyloid protein by NMR methods. They investigated that the helical intermediation of $A\beta_{1-40}$ is crucial aspect for the on-pathway intermediates in amyloid fibrillogeneous [19]. In addition, other experimental studies investigated the mechanism of amyloid aggregation and kinetics of amyloid fibril formation to prevent cytotoxicity and development of higher-order structures [20].

Researchers have made efforts to establish the amyloid aggregation, folding, and development from amyloid monomers to amyloid oligomers structures at atomic scale using computational methods [20,21]. For example, Thirumalai et al. have investigated Aβ amyloid aggregation and folding via computational studies using explicit solvent molecular dynamics (MD) simulations [21]. These studies revealed the important role of water-protein interactions that stabilize amyloids through hydrophobic residues. The hydrophobic characteristic allows processing of amyloid oligomer or monomer aggregations by expelling the water molecules. In similar manner, Chong et al. investigated pathological Aβ protein aggregation and folding through MD simulation in explicit solvent conditions, and calculated the hydration energy of charged amino acids and its effect on protein hydrophobicity [22,23]. For the importance of explicit solvent, Berhanu et al. [24] and Yoon et al. [25] investigated the stability and formation of hIAPP amyloid protofibrils through molecular mechanic/Poisson–Boltzmann solvent accessible (MM/PBSA) analysis, and found out that electrostatic interactions between water molecules and hIAPP are the major source of amyloid fibrillar stability. Thus, the effect of water has been recognized as a major factor in the stability of amyloids. Indeed, efforts have been made to investigate the destabilization of amyloid fibrils that may serve as a foundation to decompose the amyloid fibrils [26–28].

To analyze the stability of amyloid during folding or aggregation under explicit solvent conditions, several research groups investigated the effect of solvents on amyloid oligomers in detail. In brief, protein folding occurs in pure water due to hydrogen bonding interactions, hydrophobic characteristics and turn region, which are part of amyloid monomer structures. This turn region includes aspartic acid and lysine residues. Especially, the importance of turn region of partial fragment of Aβ amyloid protein has been on the rise through MD techniques. Using discrete molecular dynamics (DMD) simulation, Urbanc and co-workers found out that salt-bridges and hydrophobic interactions are stabilizing forces in truncated Aβ (25–35) amyloid monomer structures [29,30]. In similar manner, Shea and Wei investigated the turn region of a truncated Aβ (25–30) oligomer through replica exchange molecular dynamics (REMD) simulation in pure water and mixed solvent of water/HFIP with various temperature ranges [31]. They observed the conversion from α-helices to β-strands and the folding process through hydrogen bonding, which plays an important role in amyloid protofibrillar structure's stability. In addition, the importance of the turn region was observed by the defined secondary structure of proteins (DSSP); the β strand proportion was increased under water compared to that under mixed solvent conditions. Also, hydrogen bonding analysis was conducted in order to confirm the stability of Aβ amyloid oligomer structures over a range of temperatures [31].

Recently, Yang et al. found conformational changes of a full-length Aβ (1–42), rather than a partial amyloid oligomer structure, during atomistic scale simulations in various solvents, i.e., water, DMSO, TFE, and HFIP [32]. They found out that full-length amyloids retained their structure in TFE, HFIP, and water during 20-ns equilibrated MD simulation. In this simulation, β-strand was primarily observed in water via DSSP and conformational analysis. However, the amyloid structures were destabilized after 2 ns in DMSO. In similar manner, Mehrnejad et al. investigated the structure and dynamics of the humanin protein, and discovered a structural varia-

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