Computational study on the structural diversity of amyloid Beta Peptide (abeta(10-35)) oligomers.

ARTICLE *in* THE JOURNAL OF PHYSICAL CHEMISTRY B · APRIL 2008

Impact Factor: 3.3 · DOI: 10.1021/jp076450w · Source: PubMed

Computational Study on the Structural Diversity of Amyloid Beta Peptide ($A\beta_{10-35}$) Oligomers

Soonmin Jang[†] and Seokmin Shin*[,‡]

School of Chemistry, Seoul National University, Seoul 151-747, Korea, and Department of Chemistry, Sejong University, Seoul 143-747, Korea

Received: August 10, 2007; In Final Form: January 11, 2008

We studied the oligomerization of Alzheimer amyloid beta peptide ($A\beta$) using a replica exchange molecular dynamics (REMD) simulation. The simulation was performed with $A\beta_{10-35}$ dimers, trimers, and tetramers. Extensive REMD simulations illustrated several possible oligomer conformations. As the size of the oligomer increased from a dimer to a tetramer, the number of possible configurations was reduced. We identified all the possible conformations for each oligomer and characterized their temperature dependence. It was found that the detailed structures of the oligomers, which may act as folding intermediates, are highly sensitive to the parameters of the simulation environment such as temperature and concentration. Structural diversities of $A\beta$ oligomers suggest multiple pathways of the aggregation process.

Introduction

The aggregation of amyloid beta ($A\beta$) peptide is closely related to the onset of a group of diseases known as conformational diseases, which includes Alzheimer's diseases (AD), type II diabetes, and bovine spongiform encephalopathy (BSE).[1,2] Aggregation of $A\beta$ peptides leads to the formation of a structurally well-organized amyloid fibril that shows a characteristic cross-beta X-ray diffraction pattern due to the extensive β-sheet conformation perpendicular to the fibril axis, suggesting that there is a common mechanism behind those diseases.[3,4] Understanding the detailed structural features of the $A\beta$ fibril is one of the key issues for therapeutic purposes.[5] Despite the limitations of conventional experiments in the study of the amyloid fibril structure, mainly due to its poor solubility and the difficulty of forming single crystals, the structural features of the amyloid fibril have begun to appear using various approaches.[6]

The Alzheimer $A\beta$ peptide is released from the $A\beta$ protein precursor (APP), and it has a chain length of 39 to ~43 units, with chain lengths of 40 ($A\beta_{1-40}$) and 42 ($A\beta_{1-42}$) units as the major components. The onset of $A\beta$ peptide oligomerization, after it is released from the APP, is the first step toward amyloid fibril formation. Interestingly, it is known that the amyloid oligomer itself, rather than the fibril, is more neurotoxic.[7−9] It is reported that the dimer and tetramer of the $A\beta$ peptide may act as intermediates for further fibril formation.[10] Thus, the oligomerization of the $A\beta$ peptide has become a subject of intense research recently. It was found that the formation of morphologically different, therefore of different toxicities, Alzheimer amyloid fibrils is possible with its own seeding,[11] indicating that structurally different oligomers may be involved as intermediates or templates for further fibril growth.

As a complement to experiments, computational studies can provide valuable insight into the nature of amyloid fibrils by providing direct information on the structure, stability, interaction patterns, and possible fibril formation mechanisms of the $A\beta$ protein. These studies include the characterization of prefibrillar amyloidogenic monomer peptides,[12−17] effects of mutation,[18−22] identification of intermediates and the folding pathway of the fibril formation process,[23−30] structural features and stabilities of amyloidogenic oligomers,[31−34] kinetics,[35,36] and formation of amyloid oligomers and fibrils.[25,29,37−43]

The 27 residue $A\beta_{10-35}$, a partial segment of $A\beta_{1-40}$, has been acclaimed as a good model for the study of the full-length Alzheimer beta peptides $A\beta_{1-40}$ or $A\beta_{1-42}$, partly because it has a better solubility.[44−47] It has been found[48−50] that both $A\beta_{1-40}$ and $A\beta_{1-42}$ have the same structural features as $A\beta_{10-35}$, which is an in-register parallel β-sheet with a non-β bend in the V25−G29 region (note the similar results from simulations[31]). Unlike other short strands of the full $A\beta$, in which the structure depends heavily on sequence and residue length,[51] the structural similarity of $A\beta_{10-35}$ to full-length $A\beta$ makes $A\beta_{10-35}$ one of the most interesting subjects for many $A\beta$ studies.[44,48,52] From a computational point of view, the self-assembly of $A\beta_{10-35}$ oligomers, especially oligomers of sizes of four or more, from monomeric forms is still a challenging problem mainly due to the large number of atoms involved and the extremely slow time scale required to form oligomers/fibrils. Urbanc et al.[40] performed discrete molecular dynamics (DMD) simulations with a coarse-grained model on the self-assembly of the $A\beta_{10-35}$ dimer and obtained several possible stable conformers. Han and Wu[19] observed, via a long-time molecular dynamics study, the structural displacement of monomeric $A\beta_{10-35}$ into a strand−loop−strand structure in an aqueous environment and suggested that this structure may be a possible intermediate for fibril formation. Also, from MD simulations, it has been reported that the hydrophobic interaction is an important stabilizing force and that substantial structure reorganization may be involved during $A\beta_{10-35}$ dimerization.[27]

In a previous paper,[53] we reported the observation of several possible $A\beta_{10-35}$ dimer and trimer structures and addressed their stabilities at an all-atom level. Since the $A\beta_{10-35}$ tetramer might act as one of the possible intermediates in fibril growth, the detailed structure of the tetramer and its equilibrium mixture

* Corresponding author. E-mail: sshin@snu.ac.kr.
[†] Sejong University.
[‡] Seoul National University.

10.1021/jp076450w CCC: $40.75
Published on Web 02/28/2008 PAGE EST: 5.8

with other small oligomers (monomer, dimer, and trimer) are of particular interest. The main feature obtained from the previous study was that the resulting dimeric and trimeric conformers were mainly composed of a double β-sheet with a bend around residues 25−29 and that several interlocking structures of the bent double β-sheets were observed together with some α-helical segments. The question is as to whether all the different dimeric or trimeric conformers found from dimer and trimer simulations would survive in the oligomerization of the tetramer, which might be one of the important intermediate steps in fibril formation. The temperature dependence of equilibrium composition and stability for tetrameric Aβ_{10-35} also is a very interesting problem that needs to be answered. In this study, we report our observations of the self-assembly of Aβ_{10-35} tetramers at the atomic level using an extensive replica exchange molecular dynamics (REMD) simulation.[54]

Model and Simulation Methods

The aggregation of proteins is usually a very slow process. This is not only because proteins are required to have proper orientations with respect to each other but also because each protein/peptide needs to undergo suitable conformational changes before aggregation. The computational study of this aggregation process as it is under the unconstrained conditions of the atomic level is extremely expensive. One of the possible computational approaches to overcome this problem is to use a very efficient sampling scheme, whereby the simulation trajectory is kept from becoming trapped in local potential energy minima. The replica exchange method (REM, i.e., the parallel tempering method) is one of the most powerful sampling schemes, and it has been used widely over a range of problems. We have used this scheme to accelerate the overall self-assembling process (aggregation) of Aβ_{10-35} oligomers.

The overall simulation method is described in ref 53. We employed the REMD simulation with protocols by Sugita and Okamoto[54] as implemented in the MD simulation package AMBER8.[55] The all-atom param96 force field with generalized Born solvent area correction (GBSA) implicit solvation model (mode II)[56] was used in this study. The starting conformation of each Aβ_{10-35} strand was taken from the NMR structure (1HZ3).[52] The REMD simulation was performed for three different systems (i.e., having two, three, and four copies of the Aβ_{10-35} strand). With regard to the simulation box, the whole system was confined within an imaginary spherical wall[39] with a radius of 45 Å for the dimer and 50 Å for both the trimer and the tetramer, where for atoms beyond the given boundary distance from the center of mass of the system, the attracting harmonic force (force constant is 1 kcal/mol) centered at that boundary position kept the molecules from flying apart from each other. The distance between each Aβ_{10-35} strand was about 25 Å initially. Considering that the end-to-end distance of Aβ_{10-35} was about 27 Å, this separation provided sufficient space for the overall tumbling of each Aβ_{10-35} molecule. The number of replicas was set to 32 with a temperature range of 283.02 to ∼404.70 K, which yielded a replica exchange acceptance ratio of 20 to ∼40%. The initial 100 ps of the REMD simulation was performed with no replica exchange, to allow structural decorrelation. The REMD simulation time of each replica was 145 ns for the dimer, 150 ns for the trimer, and 112 ns for the tetramer. The simulation time step was 2.0 fs with a bond constraint on the hydrogen atom using SHAKE. The replica exchange interval was set to 0.4 ps, and the nonbonded cutoff distance was maintained as 15.0 Å throughout the simulation. The conformation of each replica trajectory was saved every 200 fs.

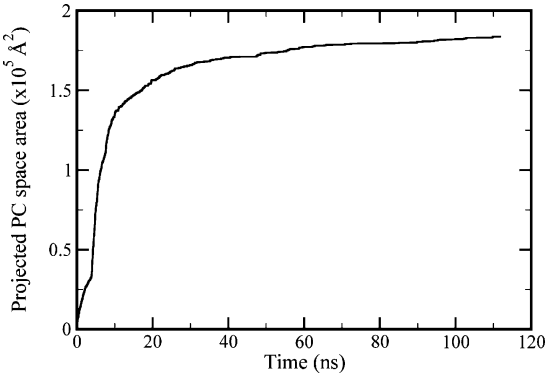

Figure 1. Time evolution of the sampled configuration space area, as measured using projections of the trajectory into the first two major principal components, illustrates a quantitative measure of the convergence of the REMD simulation.

Results and Discussion

For the purpose of analyzing the ensemble of trajectories in REMD simulations, it is important to make sure that the simulation has reached reasonable convergence, yielding a complete sampling of the configuration space of the system. We performed a principal component (PC) analysis with backbone atoms and monitored the time evolution of the sampled PC space as the REMD simulation proceeded. The time evolution of the sampled configuration space area, measured using projections of the trajectory into the first two major PCs, can serve as a measure of REMD convergence.[57,58] The two-dimensional PC space was discretized by a 60 × 60 grid, and the number of cells was counted to calculate the sampled space. In Figure 1 is plotted the time evolution of the sampled PC space area at 300 K. It is shown that the sampled PC space increases rapidly during the early stage of the simulation and that it begins to approach asymptotically a constant value. It can be argued that the simulation begins to converge after 50 ns and that the system has reached reasonable quasi-equilibration for the later part of the trajectory.

During the time scales of our REMD simulations, we observed the spontaneous self-assembly of oligomers of Aβ_{10-35} peptides. As reported in a previous work,[53] the results of REMD simulations illustrated the overall structural features associated with the formation of Aβ oligomers. For the oligomers up to tetramers, each Aβ_{10-35} unit formed two β-strands joined by a turn region, and the assembly of such bent double β-strands exhibited several different interlocking patterns. Depending on temperature, the monomeric form of Aβ_{10-35} coexisted with other possible oligomers. We defined that any two strands are in contact if the minimum distance between the two, in other words, the Cα distance between any two residues in the range of 19 to ∼35 units from the two strands, is within 5.5 Å. This is somewhat arbitrary criterion, but we graphically checked that it provides a reasonable criterion and distinguishes high-temperature situations where only random structureless contact may exist. For dimer simulations, essentially all strands exist as a dimeric form at low temperatures (283 K), and this dimer form remains up to 350 K. Above 350 K, almost all strands exist only as a monomer. The dimeric conformers above this temperature are highly unfolded and structureless even though they are in close contact with each other. As for the trimer simulations, trimeric conformers are in equilibrium with dimeric and monomeric structures at low temperatures up to 320 K

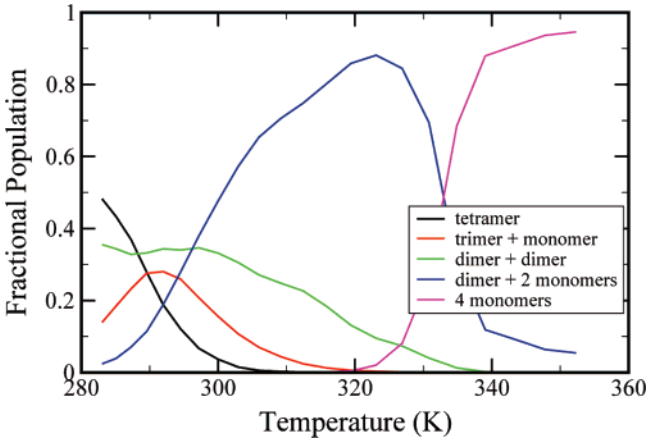

Figure 2. Temperature-dependent populations of tetrameric, trimeric, dimeric, and monomeric conformers in tetramer simulations.

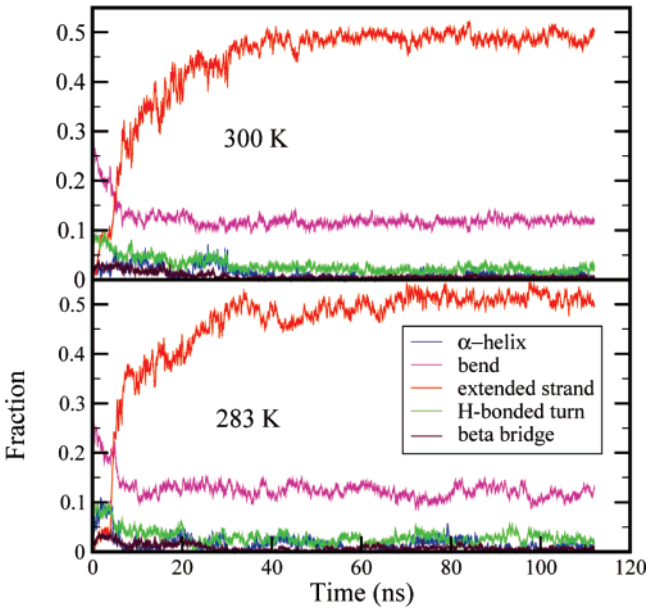

Figure 3. Time profile of secondary structure contents for the tetramer simulations at 300 and 283 K.

where the dimer concentration peaks. Again, the [dimer + monomer] conformers above 350 K have random unfolded structures.

The distribution of oligomers and the monomer as a function of temperature, for the last 4 ns of tetramer simulation trajectories, is shown in Figure 2. We observed mixed conformers of [tetramer], [trimer + monomer], [dimer + dimer], [dimer + two monomers], and [four monomers]. This population distribution remains roughly the same all the way from 95 ns of REMD simulations to the rest of the tetramer simulation (112 ns). These observations, along with the time profiles of secondary structures from DSSP analysis[59] at two different temperatures (300 and 283 K), as shown in Figure 3, indicate that our REMD has reached a quasi-equilibrium, consistent with the result of the sampled PC space shown in Figure 1. However, this may not serve as a strict convergence criterion, and the full equilibration may take considerably more time due to the nature of extremely slow amyloid formation. Like trimer simulations, the monomeric conformer dominates at temperatures higher than 320 K, and the trimeric conformer exists only below this temperature. It is noted that the concentration of the trimeric conformer is at its maximum at 290 K, below which the tetrameric conformer dominates the trimeric conformer. We

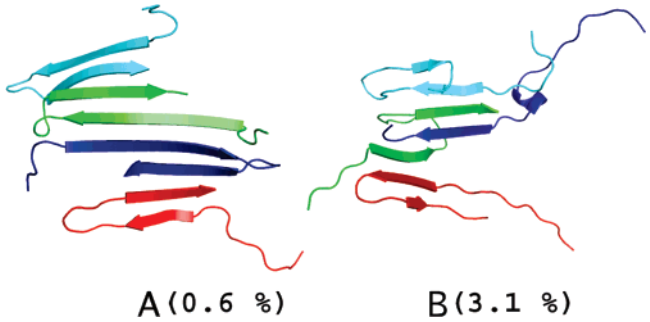

Figure 4. Structures of two major tetrameric conformers observed in tetramer simulations at 300 and 283 K.

also note that the [dimer + dimer] concentration is somewhat larger than the trimeric conformations. In the spirit of unfolding simulations for single chain proteins, one may examine the aggregation process by performing disaggregation simulations at high temperatures. Even though we did not actually perform the disaggregation simulations, our REMD simulations results on temperature dependence may suggest a possible aggregation process. At high temperatures, only unstructured monomers are present. As the temperature is lowered, dimers can be formed. Some of these dimers can grow into trimers by adding a single monomer. The formation of the tetramer can be performed either by combining two dimers or adding a single monomer to a trimer. These two processes occur at the same time; however, the [dimer + dimer] association seems to be the more prominent pathway according to our simulations.

We have shown previously that nine and six structurally different conformers were found for the dimer and trimer simulations, respectively.[53] As for the simulation with tetramers, we found that only two structurally different tetrameric conformers are possible, indicating that as the cluster size increases, the number of possible conformers is reduced, although some confinement/concentration effects cannot be ruled out.[60] These findings may be expected since the relative stabilities among different conformers become pronounced as the cluster size is increased and some of the conformers are becoming inaccessible. The two different tetramers (A and B) are shown in Figure 4. The orientations of the pair of strands show both parallel and antiparallel conformations. It is noted that a partial helix conformation is observed in conformer B. The time evolution of the secondary structure (Figure 3) also shows non-zero α-helix content throughout the simulation, suggesting that the α-helix could be a possible intermediate of amyloid formation. However, tetramer simulations as well as dimer and trimer simulations showed that not all conformers require α-helix conformation as an intermediate. The more ordered conformer A is favored over the less ordered conformer B at low temperature (283 K), but the trend is reversed at high temperatures (300 K), which is consistent with observations in the dimer and trimer cases.[53] Very recently, Gnanakaran et al.[42] showed that dimer Aβ_{16-22} conformations have a strong temperature dependence. Our results support these findings and suggest that this tendency continues at least up to tetramers and possibly goes all the way up to the critical nuclei size acting as a seed for fibril growth. The population of each tetramer (A and B) as a function of temperature is shown in Figure 5. The relative population is reversed around 288 K, and conformer B survives up to higher temperatures. One may also interpret this result such that the conformer B is a metastable intermediate before the formation of a more ordered tetramer represented by conformer A.

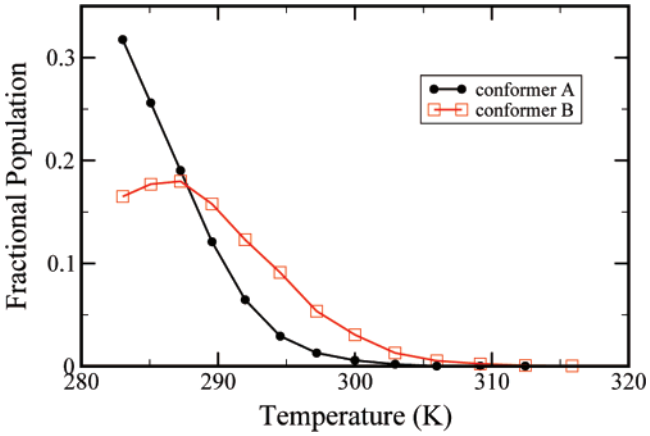

Figure 5. Temperature-dependent populations of two major tetrameric conformers observed in tetramer simulations.

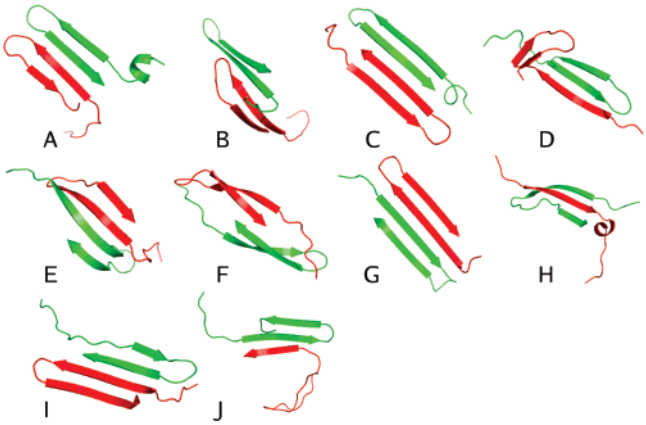

Figure 6. Various dimer conformers observed in tetramer simulations at 283 and 300 K.

One interesting question is to compare dominant dimer/trimer conformers obtained from different simulations involving different oligomers. For example, one may ask as to whether the dimer conformers observed in dimer simulations also appear in trimer or tetramer simulations. Do the trimer conformers observed in trimer simulations have similar structures to the [trimer + monomer] conformers in tetramer simulations? Some of the structures of dimers for the [dimer + monomer] conformers observed in the trimer simulation are found to be different from those observed in the dimer simulations. As for the tetramer simulations, various dimeric conformers were observed. These different dimers are from the [dimer + dimer] and [dimer + two monomers] conformers. We selected 10 topologically distinct conformations as shown in Figure 6. All of the 10 different conformers were observed at 300 K, while conformers E, H, and J were not observed at 283 K. Some dimers observed in trimer simulations were not observed in tetramer simulations, and some dimers observed in tetramer simulations were not observed in trimer and dimer simulations. To make things more complicated, some conformers (A, C, H, and J) existed only as [dimer + dimer], while some conformers (E and F) only existed as [dimer + two monomers]. The structures of trimers observed in tetramer simulations as a [trimer + monomer] are shown in Figure 7. Only two different conformers, which are different from those found in the trimer simulations, were observed at both temperatures. It is noted that both the dimer and the trimer conformers observed during the tetramer simulations were more ordered than the main conformers found in dimer and trimer simulations. These results clearly illustrate that the detailed structures of small oligomers are

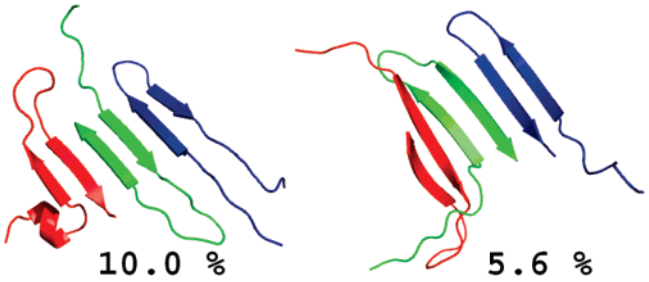

Figure 7. Two different trimer conformers observed in tetramer simulations at 283 and 300 K.

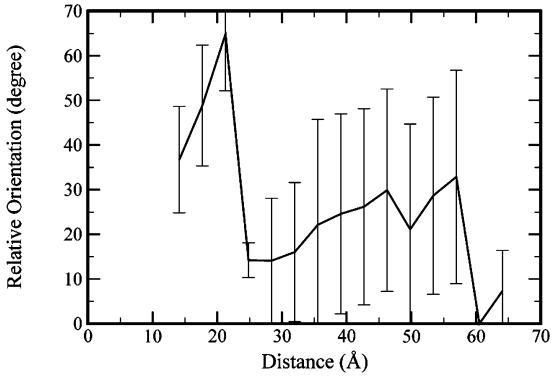

Figure 8. Relative orientational angle between the single approaching strand and the trimer at 300 K. The angle is defined between two vectors connecting the 25th and 36th Cα atoms of the approaching single strand and the center strand in the trimer.

highly sensitive to the conditions of the simulation environment,[11] such as temperature and concentration (presence of neighboring strands). Therefore, it is probable that the various oligomer conformers we have observed may simply serve as an intermediate or transient species for highly ordered fibril or large-sized oligomers. It has been suggested that even low molecular weight oligomers might have different conformational tendencies, leading to multiple pathways.[61]

The detailed mechanism of amyloid formation is largely unknown. From the extensive computer simulation of $A\beta_{16-22}$ oligomers, in which the major conformer is a simple antiparallel β-sheet, Nguyen et al.[62] showed that the oligomerization proceeded by two stages: the approach of monomers to the existing oligomer with a rapid increase of β-strand content followed by slow rearrangement of both monomer and oligomer into an in-register antiparallel form. They inferred that the assembly of other amyloid-like aggregates might share a similar scenario. Unlike the amyloid oligomer with a short extended strand, the oligomerization of $A\beta_{10-35}$, which has a bent structure in 24−27 (VGSN), might involve different or extra pathways. In an attempt to find the qualitative picture for the association of monomers and existing oligomers, we calculated the relative orientation of monomers with respect to trimers as a function of their distance in the tetramer simulations. The distance is simply defined as the distance between the center of mass of the monomer and trimer. The angle is defined between the two vectors connecting the 25th and 36th Cα atom of the approaching single strand and the center strand in the trimer. We clustered the resulting 3006 [trimer + monomer] conformations based on the center of mass distance between the approaching monomer strand and the existing trimer. Even though the relative orientation is somewhat loosely defined, it is shown that there is a sudden relative orientational change around 22 Å (Figure 8). This result suggests that the reorientation of the monomer

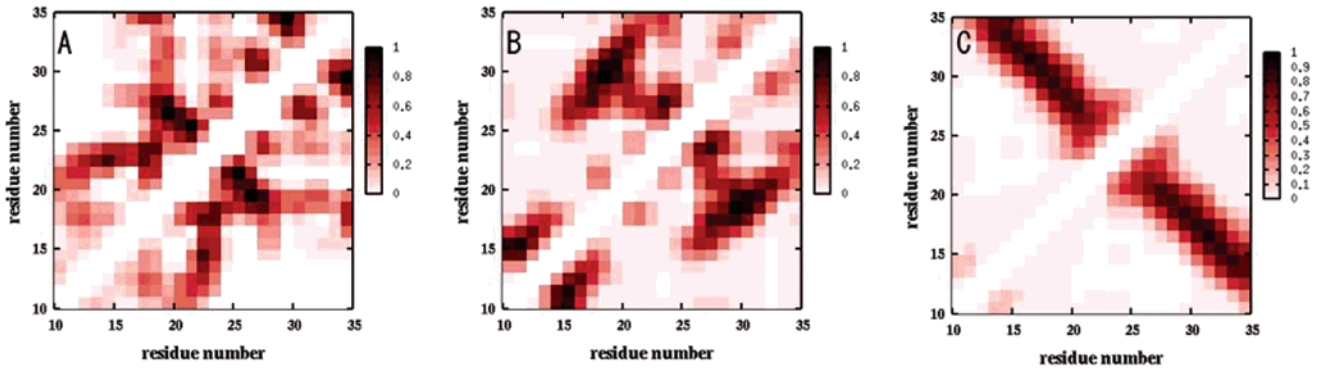

Figure 9. Aβ_{10-35} monomer contact map determined from (A) 15 NMR structures, (B) constant temperature MD simulations at 285 K, and (C) REMD simulations at 285 K. The contact maps for simulations were constructed from the last 2 ns of the trajectory (10 000 frames) out of 48 ns constant temperature MD simulations and 20 ns REMD simulations, respectively.

is an important step during the docking of a monomer to the growing oligomers.

As in other computational studies on the dynamics of protein folding and aggregation, the results of the present study have some limitations, in particular, due to the use of a specific force field. The AMBER parm96 force field is known to yield a rather high β-strand propensity,[63] which might lead to a somewhat higher degree of ordered β-sheet structures. In fact, our β-strand fraction from DSSP analysis is about 45%, which is quite high as compared to the experimental results of 10 to ~20%.[64] Interestingly, the β-strand content from our dimer simulation is about 40%, and it increased to ~50% in trimer simulation,[53] but no further increment was observed (~50%) in tetramer simulations. We performed a constant temperature MD simulation, starting from one of the PDB structures, at 285 K for 48 ns and a separate REMD simulation for 20 ns with an Aβ_{10-35} monomer. The increased β-strand propensity also can be observed in our monomeric Aβ_{10-35} simulations. The resulting contact maps from these simulations are shown in Figure 9 along with those from 15 NMR conformations. A pair of residues is in contact if their heavy atom distance is within 5.4 Å, and a contact score of 1.0 is assigned to the distance matrix. If the distance is longer than 5.4 Å or the pair is a neighboring pair (less than three residues away), no contact score is assigned.[65] It is not surprising that the constant temperature results show some structural differences from NMR structure.[19] Similar differences have been noted in recent studies on wild-type and mutant Aβ monomer/dimer simulations.[22] It was argued that there exist subtleties in comparing the results from circular dichroism and NMR experiments and those obtained from the simulations. The discrepancies in secondary structural properties might be due to the limitations of the GB solvation model and/or the parm96 force field. It has been pointed out that the generalized Born (GB) force field tends to exhibit somewhat unbalanced α/β propensities and overestimations of the salt bridge effect.[63,66] The possibility of incomplete convergence cannot be ruled out as one of the contributions to the problem. Nevertheless, the REMD results clearly show that hairpin-like long-range contact is the main feature, lacking the short-range contacts shown in Figure 2f of ref 19.

Even though we employed long-time (>100 ns) REMD as an efficient method of sampling various conformations, the simulation may not be fully converged. There is a possibility that some conformers we have observed may be transient species. The use of implicit solvation in this study also may have excluded some of the conformations since the REMD simulations of the Aβ_{16-22} dimer showed that some conformations required an explicit water network to properly stabilize their structures.[42] It has been noted that the expulsion of discrete water molecules (desolvation) around D23 and K28, leading to the formation of a D23−K28 salt bridge, could play an important role in Aβ oligomerization, especially at early stages of aggregation,[67,68] illustrating possible shortcomings of the implicit solvation model. Despite these limitations, the REMD simulations of the Aβ_{10-35} dimer, trimer, and tetramer indicate that, depending on the detailed environments, various forms of dimeric conformers are possible, while only a limited number of trimeric and tetrameric conformers are observed. It may be argued that the number of possible conformers of critical-sized oligomers/fibrils that are in equilibrium with many small oligomers might be small, while the Aβ oligomerization process involves many folding pathways and intermediates. A systematic study of the confinement effect is needed to further support this notion.

The neurodegenerative mechanism of Alzheimer's disease is poorly understood. Possibly, neurotoxic Aβ oligomers may have several different sizes, and each of these oligomers has more than a single conformation and thereby a different toxicity. Understanding the structure and stability of these oligomers is one of the essential steps for therapeutic purposes. There may be, in fact, just a small number of simple oligomerization patterns behind this structural complexity and diversity. Recently, with β-2-micorglobulin, it was shown that highly native-like folding intermediates could be involved in amyloid aggregation pathways.[69] In this respect, it would be interesting, even though computationally challenging, to study other large-sized oligomers (such as pentamers and hexamers) even with a simple Aβ_{10-35} model and see if there are any common/distinct structural features that persist. This systematic study of size dependence might reveal information on the size and structure of the critical nucleus for fibril growth.

Acknowledgment. This work was supported by Grant R01-2006-000-10418-0 from the Basic Research Program of the Korea Science and Engineering Foundation. This work also was supported by a grant from the MarineBio 21 Project funded by the Ministry of Maritime Affairs and Fisheries of the Korean government. We appreciate generous computing time from the University Computer Center of Seoul National University.

References and Notes

(1) Kelly, J. W. *Curr. Opin. Struct. Biol.* **1998**, *8*, 101.
(2) Thirumalai, D.; Klimov, D. K.; Dima, R. I. *Curr. Opin. Struct. Biol.* **2003**, *13*, 146.

(3) Dobson, C. M. *Nature (London, U.K.)* **2003**, *426*, 884.
(4) Bucciantini, M.; Calloni, G.; Chiti, F.; Formigli, L.; Nosi, D.; Dobson, C. M.; Stefani, M. *J. Biol. Chem.* **2004**, *279*, 31374.
(5) Kelly, J. W. *FASEB J.* **1997**, *11*, 873.
(6) Zheng, J.; Ma, B. Y.; Nussinov, R. *Phys. Biol.* **2006**, *3*, 1.
(7) Klein, W. L.; Krafft, G. A.; Finch, C. E. *Trends Neurosci.* **2001**, *24*, 219.
(8) Kayed, R.; Head, E.; Thompson, J. L.; McIntire, T. M.; Milton, S. C.; Cotman, C. W.; Glabe, C. G. *Science (Washington, DC, U.S.)* **2003**, *300*, 486.
(9) Walsh, D. M.; Klyubin, I.; Fadeeva, J. V.; Cullen, W. K.; Anwyl, R.; Wolfe, M. S.; Rowan, M. J.; Selkoe, D. J. *Nature (London, U.K.)* **2002**, *416*, 535.
(10) Bitan, G.; Vollers, S. S.; Teplow, D. B. *J. Biol. Chem.* **2003**, *278*, 34882.
(11) Petkova, A. T.; Leapman, R. D.; Guo, Z. H.; Yau, W. M.; Mattson, M. P.; Tycko, R. *Science (Washington, DC, U.S.)* **2005**, *307*, 262.
(12) Sgourakis, N. G.; Yan, Y. L.; McCallum, S. A.; Wang, C. Y.; Garcia, A. E. *J. Mol. Biol.* **2007**, *368*, 1448.
(13) Armen, R. S.; DeMarco, M. L.; Alonso, D. O. V.; Daggett, V. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11622.
(14) Dedmon, M. M.; Lindorff-Larsen, K.; Christodoulou, J.; Vendruscolo, M.; Dobson, C. M. *J. Am. Chem. Soc.* **2005**, *127*, 476.
(15) Massi, F.; Straub, J. E. *J. Comput. Chem.* **2003**, *24*, 143.
(16) Bernstein, S. L.; Wyttenbach, T.; Baumketnert, A.; Shea, J. E.; Bitan, G.; Teplow, D. B.; Bowers, M. T. *J. Am. Chem. Soc.* **2005**, *127*, 2075.
(17) Borreguero, J. M.; Urbanc, B.; Lazo, N. D.; Buldyrev, S. V.; Teplow, D. B.; Stanley, H. E. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 6015.
(18) Massi, F.; Klimov, D.; Thirumalai, D.; Straub, J. E. *Protein Sci.* **2002**, *11*, 1639.
(19) Han, W.; Wu, Y.-D. *J. Am. Chem. Soc.* **2005**, *127*, 15408.
(20) Barducci, A.; Chelli, R.; Procacci, P.; Schettino, V.; Gervasio, F. L.; Parrinello, M. *J. Am. Chem. Soc.* **2006**, *128*, 2705.
(21) Haspel, N.; Zanuy, D.; Ma, B. Y.; Wolfson, H.; Nussinov, R. *J. Mol. Biol.* **2005**, *345*, 1213.
(22) Huet, A.; Derreumaux, P. *Biophys. J.* **2006**, *91*, 3829.
(23) Wei, G. H.; Mousseau, N.; Derreumaux, P. *Biophys. J.* **2004**, *87*, 3648.
(24) Santini, S.; Wei, G. H.; Mousseau, N.; Derreumaux, P. *Structure* **2004**, *12*, 1245.
(25) Santini, S.; Mousseau, N.; Derreumaux, P. *J. Am. Chem. Soc.* **2004**, *126*, 11509.
(26) Klimov, D. K.; Thirumalai, D. *Structure* **2003**, *11*, 295.
(27) Tarus, B.; Straub, J. E.; Thirumalai, D. *J. Mol. Biol.* **2005**, *345*, 1141.
(28) Melquiond, A.; Boucher, G.; Mousseau, N.; Derreumaux, P. *J. Chem. Phys.* **2005**, *122*, 174904.
(29) Paci, E.; Gsponer, J.; Salvatella, X.; Vendruscolo, M. *J. Mol. Biol.* **2004**, *340*, 555.
(30) Wu, C.; Lei, H. X.; Duan, Y. *J. Am. Chem. Soc.* **2005**, *127*, 13530.
(31) Ma, B. Y.; Nussinov, R. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 14126.
(32) Li, L. P.; Darden, T. A.; Bartolotti, L.; Kominos, D.; Pedersen, L. G. *Biophys. J.* **1999**, *76*, 2871.
(33) Zanuy, D.; Gunasekaran, K.; Ma, B. Y.; Tsai, H. H.; Tsai, C. J.; Nussinov, R. *Amyloid* **2004**, *11*, 143.
(34) Meinke, J. H.; Hansmann, U. H. E. *J. Chem. Phys.* **2007**, *126*.
(35) Nguyen, H. D.; Hall, C. K. *J. Biol. Chem.* **2005**, *280*, 9074.
(36) Hwang, W.; Zhang, S. G.; Kamm, R. D.; Karplus, M. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12916.
(37) Cecchini, M.; Rao, F.; Seeber, M.; Caflisch, A. *J. Chem. Phys.* **2004**, *121*, 10748.
(38) Nguyen, H. D.; Hall, C. K. *J. Am. Chem. Soc.* **2006**, *128*, 1890.
(39) Baumketner, A.; Shea, J. E. *Biophys. J.* **2005**, *89*, 1493.
(40) Urbanc, B.; Cruz, L.; Ding, F.; Sammond, D.; Khare, S.; Buldyrev, S. V.; Stanley, H. E.; Dokholyan, N. V. *Biophys. J.* **2004**, *87*, 2310.
(41) Favrin, G.; Irback, A.; Mohanty, S. *Biophys. J.* **2004**, *87*, 3657.
(42) Gnanakaran, S.; Nussinov, R.; Garcia, A. E. *J. Am. Chem. Soc.* **2006**, *128*, 2158.
(43) Tsai, H. H.; Reches, M.; Tsai, C. J.; Gunasekaran, K.; Gazit, E.; Nussinov, R. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 8174.
(44) Lee, J. P.; Stimson, E. R.; Ghilardi, J. R.; Mantyh, P. W.; Lu, Y. A.; Felix, A. M.; Llanos, W.; Behbin, A.; Cummings, M.; Vancriekinge, M.; Timms, W.; Maggio, J. E. *Biochemistry* **1995**, *34*, 5191.
(45) Esler, W. P.; Stimson, E. R.; Ghilardi, J. R.; Lu, Y. A.; Felix, A. M.; Vinters, H. V.; Mantyh, P. W.; Lee, J. P.; Maggio, J. E. *Biochemistry* **1996**, *35*, 13914.
(46) Young, J. K.; Anklin, C.; Hicks, R. P. *Biopolymers* **1994**, *34*, 1449.
(47) Lau, T. L.; Barnham, K. J.; Curtain, C. C.; Masters, C. L.; Separovic, F. *Aust. J. Chem.* **2003**, *56*, 349.
(48) Antzutkin, O. N.; Leapman, R. D.; Balbach, J. J.; Tycko, R. *Biochemistry* **2002**, *41*, 15436.
(49) Balbach, J. J.; Petkova, A. T.; Oyler, N. A.; Antzutkin, O. N.; Gordon, D. J.; Meredith, S. C.; Tycko, R. *Biophys. J.* **2002**, *83*, 1205.
(50) Benzinger, T. L. S.; Gregory, D. M.; Burkoth, T. S.; Miller-Auer, H.; Lynn, D. G.; Botto, R. E.; Meredith, S. C. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 13407.
(51) Thompson, L. K. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 383.
(52) Zhang, S.; Iwata, K.; Lachenmann, M. J.; Peng, J. W.; Li, S.; Stimson, E. R.; Lu, Y.; Felix, A. M.; Maggio, J. E.; Lee, J. P. *J. Struct. Biol.* **2000**, *130*, 130.
(53) Jang, S.; Shin, S. *J. Phys. Chem. B* **2006**, *110*, 1955.
(54) Sugita, Y.; Okamoto, Y. *Chem. Phys. Lett.* **1999**, *314*, 141.
(55) Case, D. A.; Darden, T. A.; Cheatham, T. E. I.; Simmerling, C. L.; Wang, J.; Duke, R. E.; Luo, R.; Merz, K. M.; Wang, B.; Pearlman, D. A.; Crowley, M.; Brozell, S.; Tsui, V.; Gohlke, H.; Mongan, J.; Hornak, V.; Cui, G.; Beroza, P.; Schafmeister, C.; Caldwell, J. W.; Ross, W. S.; Kollman, P. A. *AMBER8*; University of California, San Francisco: San Francisco, 2004.
(56) Case, D. *Abstr. Pap. Am. Chem. Soc.* **2003**, *225*, 779.
(57) Kubitzki, M. B.; de Groot, B. L. *Biophys. J.* **2007**, *92*, 4262.
(58) Zhang, W.; Wu, C.; Duan, Y. *J. Chem. Phys.* **2005**, *123*, 154105.
(59) Kabsch, W.; Sander, C. *Biopolymers* **1983**, *22*, 2577.
(60) Yang, S. C.; Levine, H.; Onuchic, J. N. *J. Mol. Biol.* **2005**, *352*, 202.
(61) Goldsbury, C.; Frey, P.; Olivieri, V.; Aebi, U.; Muller, S. A. *J. Mol. Biol.* **2005**, *352*, 282.
(62) Nguyen, P. H.; Li, M. S.; Stock, G.; Straub, J. E.; Thirumalai, D. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 111.
(63) Yoda, T.; Sugita, Y.; Okamoto, Y. *Chem. Phys. Lett.* **2004**, *386*, 460.
(64) Walsh, D. M.; Hartley, D. M.; Kusumoto, Y.; Fezoui, Y.; Condron, M. M.; Lomakin, A.; Benedek, G. B.; Selkoe, D. J.; Teplow, D. B. *J. Biol. Chem.* **1999**, *274*, 25945.
(65) Kazmirski, S. L.; Li, A. J.; Daggett, V. *J. Mol. Biol.* **1999**, *290*, 283.
(66) Nymeyer, H.; Garcia, A. E. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 13934.
(67) Tarus, B.; Straub, J. E.; Thirumalai, D. *J. Am. Chem. Soc.* **2006**, *128*, 16159.
(68) Han, W.; Wu, Y. D. *Proteins: Struct., Funct., Bioinf.* **2007**, *66*, 575.
(69) Jahn, T. R.; Parker, M. J.; Homans, S. W.; Radford, S. E. *Nat. Struct. Mol. Biol.* **2006**, *13*, 195.