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International journal of Advanced Biological and Biomedical Research

Volume 1, Issue 11, 2013: 1512-1517

Study of Cis–trans Isomerization Mechanism of [3-(3-Aminomethyl) Phenylazo] Phenyl acetic Acid as a Causative Role in Alzheimer Using Density Functional Theory

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ABSTRACT

Amyloid-β (Aβ) self-assembly into cross-β amyloidfibrils is implicated in a causative role in Alzheimer's disease pathology.Uncertainties persist regarding the mechanisms of amyloid self assembly and the role of metastable prefibrillar aggregates. Aβ fibrilsfeature a sheet-turn-sheet motif in the constituent β-strands; as such, turn nucleation has been proposed as a rate-limiting step in the self assembly pathway. Herein, we report the use of an azobenzene β-hairpin mimetic to study byUsing Density Functional Theory the role turn nucleation plays on Aβ self assembly.[3-(3-Aminomethyl) phenylazo] phenyl acetic acid (AMPP)was incorporated into the putative turn region of Aβ42 to elicit temporal control over Aβ42 turn nucleation; it was hypothesized that self-assembly would be favored in the cis-AMPP conformation if β-hairpin formation occurs during Aβ self-assembly and that the trans-AMPP conformer would display attenuated fibrillization propensity. It was unexpectedly observed that the trans-AMPP Aβ42Additionally, cis-trans photo isomerization resulted in rapid formation of native-like amyloid fibrils and trans−cis conversion in the fibril state reduced the population of native-like fibrils. Thus, temporal photo control over Aβ turn conformation providessignificant insight into Aβ self-assembly.

Key words: Amyloid-β, turn nucleation, Alzheimer's disease, β-turn, amyloid fibrils, azobenzene photoswitch, DFT, B3lYP.

INTRODUCTION

Amyloid-β (Aβ) is a 39−43 amino acid peptide that is the major constituent of the neurotic plaques that are hallmarks of Alzheimer's disease (AD).(Haass, 1992) Aβ is cleaved fromthe amyloid precursor protein (APP) and undergoes a series ofself-association events that lead to the formation of oligomericaggregates and, ultimately, cross-β fibrils.(Hardy, 2002) Evidence suggests that soluble, prefibrillar oligomers, and not mature fibrils, arethe toxic congeners in the AD brain.(Walsh, 2002) Despite mounting evidence that implicates oligomers as the more cytotoxiccongener of AD, Aβ oligomer structure−function studies havebeen impeded by the transitory nature of these species. This isdue to the strong propensity for oligomers to self-associate intomore thermodynamically stable cross-β fibrils.(Bucciantini, 2002) It is therefore necessary to devise methods and conditions tocontrol the folding pathway to gain insight into the structure−function activity of these species on AD pathology (Ahmed, 2010) .The structure of Aβ fibrils and prefibrillar intermediates has been extensively studied.(Petkova,

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2002)Solid-state NMR studies andmolecular dynamics simulations on Aβ40 indicate that fibrilsare composed of a cross-β morphology that features a sheet turn-sheet motif, with the turn region comprising residues (Miller, 2009). proposed a similar structure inAβ42 fibrils, with a bend encompassed by residues 26 through(Sciaretta, 2005)NMR analysis of monomeric Aβ structures suggests that abend region between residues(Tomaselli, 2006) connects N-terminal andC-terminal helices under membrane-mimetic conditions.(Crescenzi, 2002)Smith et al. have identified a turn in Aβ42 oligomers betweenResidues(Lazo, 2005) and(Beharry, 2011), and a turn flanked by a D23/K28 saltbridge in the fibril structure.12 Collectively, these data suggestthat turn formation within early folding intermediates of Aβmay nucleate fibrillogenesis by facilitating α-helix → β-sheetoligomer → β-sheet fibril transitions.Turn nucleation in the (Tomaselli, 2006) region of Aβ has beenproposed to be an early folding event in Aβ fibrilnucleation.(Lazo, 2005) Turn nucleation has been probed experimentallyby restricting the turn region with a lactam heterocyclic formed by the condensation of D23 and K28 into an amidebond; enforcing the turn led to accelerated rates of self assembly.(Sciaretta, 2005)Recently, the structure of a β-hairpin conformerstabilized by an affibody ligand was reported; it was proposedthat a similar hairpin structure may be an early intermediateduring Aβ self-assembly.(Hoyer, 2008) Based on the hypothesis that β-hairpin formation is a rate-limiting step in Aβ fibril self assembly, we sought a structural probe that would enablereversible temporal control of Aβ turn nucleation in order toperturb the equilibrium of early structural conformers of Aβ thatare relevant to self-assembly events. It was reasoned that thistype of structural probe would provide significant insight intothe possible role of turn nucleation in Aβ self-assembly andcytotoxicity.Herein, we report the incorporation of a photo switch able turn mimetic into the turn region of Aβ42 to elicit temporalcontrol of turn nucleation. Azobenzene moieties have beenused extensively to perturb the tertiary and quaternary structureof peptides.(Aemissegger, 2007) We chose to use the azobenzene derivative [3-(3-aminomethyl)phenylazo] phenylacetic acid (AMPP) (Figure1)which was developed specifically as a β-hairpinmimetic.(Krautler, 2005) AMPP can be selectively photo isomerized in to cis or trans conformations; the cis conformer has been shown tonucleate β-hairpin turns in the context of peptides.(Dong, 2006) Wehypothesized that nucleating the turn in Aβ42 using the AMPP photo switch would nucleate fibrillization. We conjectured that, in the trans-conformation, the turn region would lie in anextended conformation that precludes efficient self-assembly.These hypotheses were explored by incorporation of AMPPinto the (Sandberg, 2010) region of Aβ42 as either a two- or three-aminoacid substitution. It was found that the self-assembly of AMPPcontainingAβ42 mutants was affected strongly by AMPPconformation. Unexpectedly, the trans-conformer readilyassembled into fibrils that was indistinguishable from wild type in nearly every aspect, including cytotoxicity. Conversely,cis-AMPP conformers assembled rapidly into aggregates thatwere dissimilar from typical Aβ42 cross-β amyloid. The cis-AMPP aggregates were sediment able, but non fibrillar and nontoxic under incubation conditions that favor either oligomerof fibril formation. Photo isomerization from cis → Trans led torapid fibrillogenesis from these nonfibril aggregates. Thisprocess could be reversed by trans → cis photo isomerization.Collectively, these results reveal that AMPP incorporated intothe sequence of an amyloidogenic peptide can be used toreversibly manipulate early folding events during fibrilnucleation. Aβ mutants that adopt stable β-turns formaggregate structures that are unable to enter folding pathwaysleading to cross-β fibrils and cytotoxic prefibrillar intermediates.

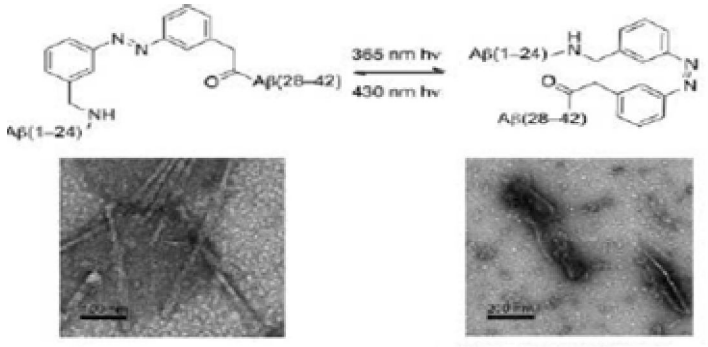

Fig.1. Photoisomerization of Amyloid-β (azobenzene derivatives)

Methods

Therefore this study aim to investigate the energetics of the initial step of cis–trans transformation for the [3-(3-Aminomethyl)phenylazo] phenylacetic acid. The B3LYP/6-31G electronic structure methods are employed to calculate the energies of the four lowest lying singlet states as a function of the reaction coordinate. In order to elucidate the mechanism of initial step in Alzheimer's phenomenon, One-dimensional potential energy curves for the isomerization of (AMPP) isomerization. From N9=N10 cis-forms to Trans forms, have been calculated by means of time-dependent density functional theory (TD-DFT) calculations. In this study, the optimization of key molecules in cis and Trans isomers of molecules Azobenzene last stage is optimal for the case file (gjf) is stored. Then save the file (gjf) with the following procedure Based Td-Series 6 -31 G and changing the solvent from the gas phase to the chloroform was ordered to pay the program Gaussian 09. In this study, the optimization of key molecules in cis and Trans isomers of molecules Azobenzene last stage is optimal for the case file (gjf) is stored. Then save the file (gjf) with the following procedure Based Td-Series 6 - 31 G and changing the solvent from the gas phase to the chloroform was ordered to pay the program Gaussian 09 For the study of electron donor and electron binding functional groups that can act as deadly as the first two The strongest electron-donor and electron- acceptor molecule is chosen as the most powerful killer electrons in the molecule NO2 and NH2 molecules were selected as the most powerful electron donor. This section also save the last Phase optimized molecular key in gjf. and procedures are followed DFT Series Base 6-31G and the binding of molecules electrons acceptor instead substituted C8 and C14 to the implementation of the two Gaussian 09 is explains. Substituent was chosen because it is the closest to our desired rotation angle N9 = N10 has Excited state with the excited state of the molecule Azobenzene resources section of the potential energy curve to obtain the rotation angle is Excited-state molecules Azobenzene To obtain Azobenzene excited state molecules by changing the type of work and energy to command mode (TD) Basic Series 6-31G and chose twelve of them in 24 states and twelve Triplet .and Singlet is to describe the implementation of the Gaussian 09 Molecules in the excited state Azobenzene angle After obtaining the excited state before exiting the stage or output it to file gjf. we are way New stores and phase angle of the molecules with a range of 10 degrees to 180 degrees to study the changes in Choose the type of work and energy to the TD-DFT Series 6-31G. Fig 2and 3.

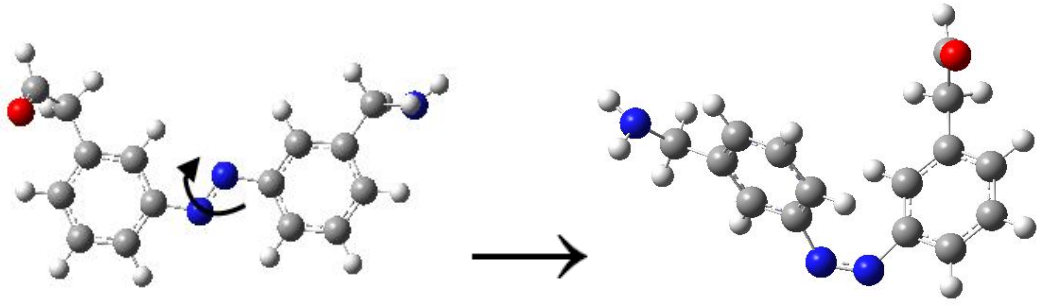

Figure 2.Cis isomers of the three-dimensional structure of molecules Azobenzene
Figure 3.Trans isomers of the three-dimensional structure of molecules Azobenzene

Results and Discussion

This is because the molecules Azobenzene mode S2, S0 ground state energy is generated at the time of return. Energy consumption by changing the cis or trans isomers is reversed .Azobenzene optical molecular switch due to certain wavelengths of light and isomers are cis to trans And trans Namespace transformed into the cis. This theory suggests that when the molecule is in the excited state by changing the amount of energy an electron donor and electron-lethal substitutions in the Azobenzene derivatives can alter the course of isomerization. Which suggests that the excited the electron donor groups connected to the Trans isomer Azobenzene can decay more rapidly than the excited Trans Azobenzene through the rotation of the N=N bond. The commutated result indicate that the transition state of the isomerization in the first excited state is located at N9–N10=90.5, where N9–N10 means twist angle around the N9=N10 double bond of (AMPP).

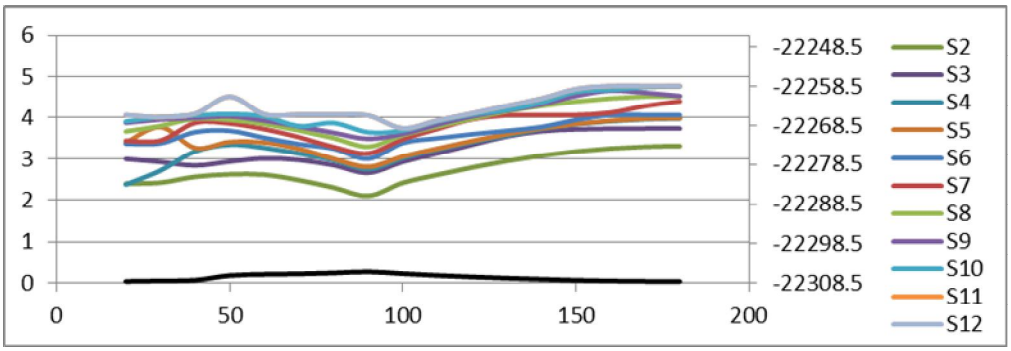

Figure4.According to the tables and charts above, we notice that the first excitation occurred in the S2 linkBecause at this point is the lowest energy barrier and Figure S2 lowest energy differences with graphs S0 (ground state) is capable of.

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