Conformations and Aggregation of Alzheimer’s Disease Peptides Studied by Ion Mobility

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The amyloid beta protein exists in two alloforms: (Aβ40) and (Aβ42). Even though Aβ42 differs from Aβ40 only in two additional C-terminal residues (I and A) it is the primary constituent of Alzheimer’s related plaques. Recent studies indicate Aβ42 is highly toxic at nanomolar levels and forms fibrils at a much faster rate than Aβ40.1 Further, current research suggests that the soluble oligomeric forms of Aβ42 are the toxic agents, not the fibrils, and are the major players of neurodegeneration in AD patients. Recent results from Teplow’s lab show the mutation Aβ42-F19P abolishes aggregation and fibril formation.2 Recent work at UCSB indicates that Aβ42(wt) and Aβ42-F19P have very similar mass spectra for the fresh sample but after incubation for 48 hours a large minus 5 charged dimer peak appears in the Aβ42-F19P mass spectrum but not in Aβ42(wt). The arrival time distribution (ATD) of the -5 dimer is bimodal indicating 2 separate dimer conformations. The more compact species (D1) has a cross section of over 10% smaller than the more extended conformer (D2). Above 300K, D3 begins to dissociate, disappearing by 400K. Near 430K D2 begins to dissociate near 430K, disappearing near 500K. Comparison with the mass spectrum suggests D2 may dissociate preferentially although some isomerization to D1 cannot be excluded. Two dimer conformations in the minus 6 charge state are also observed, in this case for both Aβ42(wt) and Aβ42-F19P. In this instance, D3, is always significantly smaller than D2. The ATD also indicates the presence of the minus 3 monomer which grows in relative abundance as either temperature or injection voltage is raised. Analysis of all the data suggests D3 closely resemble the solution conformation while D2 is the favored solvent free conformation. Molecular modeling is yet complete but preliminary structures of the relevant monomer and dimer species have been determined.

1. Barrow CJ & Zagorski MG, (1): 330-335(2003) 2. Bitan et al, 3. Recent work at UCSB indicates that Aβ42(wt) and Aβ42-F19P have very similar mass spectra for the fresh sample but after incubation for 24 hours a large minus 5 charged dimer peak appears in the Aβ42-F19P mass spectrum but not in the Aβ42(wt). The arrival time distribution (ATD) of the -5 dimer is bimodal indicating 2 separate dimer conformations. The more compact species (D1) has a cross section of over 10% smaller than the more extended conformer (D2). Above 300K, D3 begins to dissociate, disappearing by 400K. Near 430K D2 begins to dissociate near 430K, disappearing near 500K. Comparison with the mass spectrum suggests D2 may dissociate preferentially although some isomerization to D1 cannot be excluded. Two dimer conformations in the minus 6 charge state are also observed, in this case for both Aβ42(wt) and Aβ42-F19P. In this instance, D3, is always significantly smaller than D2. The ATD also indicates the presence of the minus 3 monomer which grows in relative abundance as either temperature or injection voltage is raised. Analysis of all the data suggests D3 closely resemble the solution conformation while D2 is the favored solvent free conformation. Molecular modeling is yet complete but preliminary structures of the relevant monomer and dimer species have been determined.

3. Jarrett JT et al.
Figuers Top Right: ATDs of Corrsponding charge states in the mass spectra shown in Figure 5. All ATD's display multiple features which are assigned to different structural aggregates and conformations. a) Experimental ATD for the -3 monomer/-6 dimer for Aβ42(wt) at low and high injection energies reveal 3 structures (gray). Also shown in yellow (-6 dimer) and orange -3 monomer are model structure distributions.

b) ATD for -3 charge state of Aβ42-F19P at low injection energy. c) -5 dimer ATD for Aβ42-F19P which has two features. These two features have the same spacing in cross section as the low injection features seen in the -3 monomer/-6dimer.