IR-UV DOUBLE RESONANCE SPECTROSCOPY OF A COLD PROTONATED FIBRIL-FORMING PEPTIDE: NNQQNY·H^+

ANDREW F DeBLASE, CHRISTOPHER P HARRILAL, PATRICK S. WALSH, SCOTT A McLUCKEY, TIMOTHY S. ZWIER, *Department of Chemistry, Purdue University, West Lafayette, IN, USA*.

Protein aggregation to form amyloid-like fibrils is a purported molecular manifestation that leads to Alzheimer's, Huntington's, and other neurodegenerative diseases. The propensity for a protein to aggregate is often driven by the presence of glutamine (Q) and asparagine (N) rich tracts within the primary sequence. For example, Eisenberg and coworkers [Nature 2006, 435, 773] have shown by X-ray crystallography that the peptides NNQQNY and GNNQQNY aggregate into a parallel β-sheet configuration with side chains that intercalate into a "steric zipper". These sequences are commonly found at the N-terminus of the prion-determining domain in the yeast protein Sup35, a typical fibril-forming protein. Herein, we invoke recent advances in cold ion spectroscopy to explore the nascent conformational preferences of the protonated peptides that are generated by electrospray ionization. Towards this aim, we have used UV and IR spectroscopy to record conformation-specific photofragment action spectra of the NNQQNY monomer cryogenically cooled in an octopole ion trap. This short peptide contains 20 hydride stretch oscillators, leading to a rich infrared spectrum with at least 18 resolved transitions in the 2800-3800 cm^{-1} region. The infrared spectrum suggests the presence of both a free acid OH moiety and an H-bonded tyrosine OH group. We compare our results with resonant ion dip infrared spectra (RIDIRS) of the acyl/NH-benzyl capped neutral glutamine amino acid and its corresponding dipeptide: Ac-Q-NHBn and Ac-QQ-NHBn, respectively. These comparisons bring empirical insight to the NH stretching region of the spectrum, which contains contributions from free and singly H-bonded NH_2 side-chain groups, and from peptide backbone amide NH groups. We further compare our spectrum to harmonic calculations at the M05-2X/6-31+G* level of theory, which were performed on low energy structures obtained from Monte Carlo conformational searches using the Amber* and OPLS force fields to assess the presence of sidechain-sidechain and sidechain-backbone interactions.