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The Importance of Hydrogen Bonding between the Glutamine Side-Chains to the Formation of Amyloid VQIVYK Parallel *β*-sheets. An ONIOM DFT/AM1 Study

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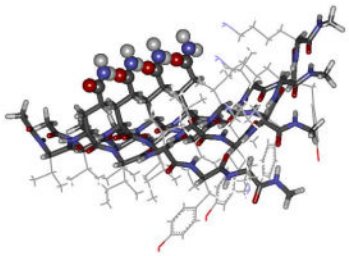
Abstract



We report DFT calculations that indicate *β*-sheet formation involving the capped amino acid sequence, VQIVYK, to be due (at least in part) to cooperative H-bonding between the glutamine side chains. The sequence, VQIVYK, has been reported to be essential for the aggregation of the protein tau into the amyloids associated with Alzheimer's disease, and has been crystallized. Sheets containing only capped Q's form cooperative H-bonds between the side chains which enhance stabilization while keeping the backbones of the individual strands close to the quasi planarity expected for a *β*-sheet. Sheets containing only capped A's cannot form H-bonds between the side-chains, do not interact cooperatively and form helical structures which deviate considerably from the quasi-planarity expected for β-sheets. Comparisons between the sheets made from capped VQIVYK's, Q's and A's illustrate the importance of the cooperative H-bonds between the Q's to the stability of tau-amyloids.

Amyloid fibrils formed from the tau protein are a symptom and probable cause of Alzheimer's disease (AD).[1-3] Mutation studies have shown the six amino acid sequence, ^{306}VQIVYK^{311}, to be essential for the formation of these fibrils.[4,5] Recent crystallographic studies on VQIVYK peptides show that long needle shaped crystals are formed from pairs of parallel *β*-sheets joined by a dry zipper-like structure formed from interdigitating side chains of adjacent *β*-strands, with the long axis of the needle perpendicular to the strands, but parallel to the chains of amidic H-bonds that form the parallel *β*-sheets.[6] These crystals can act as seeds for the formation of amyloid fibrils from tau. Similar crystals have been formed from other small peptides believed to be essential for formation of other amyloid structures.[6-8]

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Supporting Information **Available**: The complete citations for references 16 and 17, interaction enthalpies, and Cartesian coordinates and pictures of structures. This material is available free of charge via the Internet at (http://pubs.acs.org/page/jacsat/submission/authors.html).

The preferential formation of one or a few large crystals over many small crystals or microcrystalline aggregates requires cooperative enthalpic interactions in the former to overcome the entropic advantage of the latter. Amide H-bonds can be highly cooperative in the right circumstances. Both experimental[9,10] and theoretical[11] evidence indicate that polyalanine and other α-helical peptides owe their stability to cooperative enthalpic interactions. Furthermore, chains of formamides[12] can achieve stabilization enthalpies of about 13 kcal/mol, while those of the more polarizable 4-pyridone[13] can achieve stabilizations of 23 kcal/mol.

Molecular orbital (MO) studies on antiparallel *β*-sheets of polyglycine models show the H-bond cooperativity to be negated by loss of other favorable interactions.[14,15] However, polyglycine forms planar antiparallel *β*-sheets, while other peptides form the pleated sheet structure.

The glutamine (Q) residue contains an amide at the end of its side-chain, which could form chains of H-bonds that might provide stabilization in addition to that derived from the *β*-sheet backbone leading to the enthalpic H-bond cooperativity essential to crystal and probably amyloid formation. We note that the essential peptides of most (but not all) of the other crystallized amyloid-like fibrils[6] containing parallel β-sheets are rich in both glutamine and asparagine (N), which is the only other amino acid to have an amide at the end of its side-chain.

To test this hypothesis, we performed MO calculations with the GAUSSIAN 03[16] and GAUSSIAN 09[17] suite of programs, using the ONIOM[18] method with B3LYP/D95(d,p) as the high, and the semi-empirical MO AM1[19] method as the low level. We used GAUSSIAN 09 with the GAUSSAIN 03 version of AM1. The entire peptide backbone and the glutamine side-chains (containing the amide groups) comprised the high level portion, and the side-chains of the other residues comprised the low level. The methods are analogous to those previously employed for α-helices.[11] We used single point counterpoise corrections (CP) on the high level portion of the fully optimized *β*-sheets to correct energies for BSSE as the structures are too large for the CP-optimization procedure.[20] As the counterpoise and vibrational corrections to the enthalpies remain constant within 0.1 kcal/mol for addition of individual strands (beginning with the fourth) to all sheets, we used these corrections for the larger sheets, as done for chains of formamides[12] and 4-pyridones.[13]

We report calculations on the capped parallel *β*-sheets of acetyl-VQIVYK-$NHCH_3$ (Figure 1), acetyl-Q-$NHCH_3$ (Figure 2), and acetyl-A-$NHCH_3$ (Figure 3). The latter two provide smaller models for the interaction between the Q's, and comparison with a model without amide H-bonding between the Q's. These smaller models also allowed us to calculate sheets containing more stands.

As seen from Figure 4, the sheets formed from acetyl-VQIVYK-$NHCH_3$ and acetyl-Q-$NHCH_3$ (but not acetyl-A-$NHCH_3$) exhibit the hallmarks of amide H-bond cooperativity. The ΔH for adding an additional strand to the sheet becomes increasingly more negative and the H-bonding O…H distances between Qs become shorter especially near the center of the H-bonding chains as the number of stands increases.

The backbone H-bonds nearest the C-terminus within the Q-sheets shorten, in contrast to the H-bonds nearest the N-terminus. The Q-sheets have three H-bonds between each strand. One H-bond between partners can easily achieve the most stable geometry, two H-bonds can generally achieve a stable configuration without much distortion from the optimal arrangement for each H-bond. However, accommodating three or more H-bonds between the entities becomes difficult since improving one interaction will usually lead to the degradation of others. We have called this phenomenon attractive strain, as all of the interactions are attractive, yet

cannot be simultaneously optimized.[21] Attractive strain has been also observed for VQIVYK-sheets (Supporting Information), as there are a total of 8 H-bonds between strands.

Comparison between the Q (Figures 2 and 4) and A (Figures 3 and 4) sheets reveals striking qualitative and quantitative differences. The Q-sheets exhibit cooperativity reminiscent of chains of formamides[12] and 4-pyridones,[13] where the interactions become stronger as the chain or sheet grows and each type of interaction (1-2, 2-3, etc.) increases with N until it reaches its asymptotic limit. In each case the most central interaction is the strongest. The H-bond distances between the Q side-chains follow the same pattern, where each becomes shorter as the interaction becomes stronger. These H-bonds exhibit much more cooperativity than those between the backbone amides, as reflected by the change in H-bond lengths. In contrast, the interactions between the A-sheets reveal no cooperativity, the terminal (1-2) interactions are the strongest, and the central interactions remain roughly constant. The A-sheets form helical structures (Figure 3) due to the difference between the two H-bonds connecting each pair of strands (manifest by the different O…H distances). From the foregoing, one can infer the importance of the Q-Q side-chain interactions towards maintaining the relatively flat backbones of the VQIVYK sheets.

Thus, the H-bonds between the sidechains of the Q's in the VQIVYK crystals (and in the amyloids by implication) must contribute significantly to both a) the stabilization energy of formation of the sheets and b) lowering the distortion energy that would be required to flatten the sheets to conform to the conformation favorable crystal (amyloid) formation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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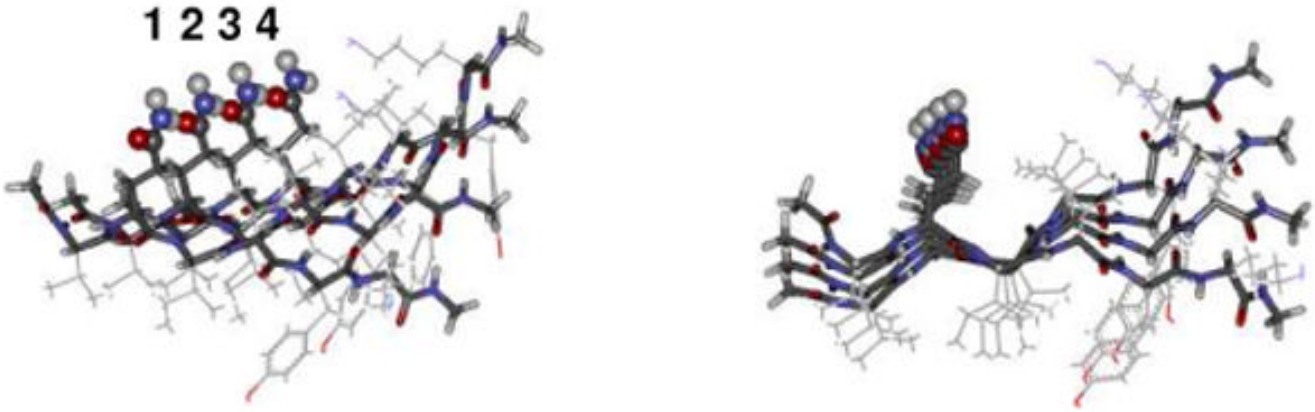

Figure 1.
Structure of the (acetyl-VQIVYK-$NHCH_3$)$_4$ parallel β-sheet. The right view is coaxial with the H-bonds between Q side-chains. The amides of the glutamine side chains are shown as balls and sticks, the backbones as tubes, and the other (non-Q) side chains as wireframe.

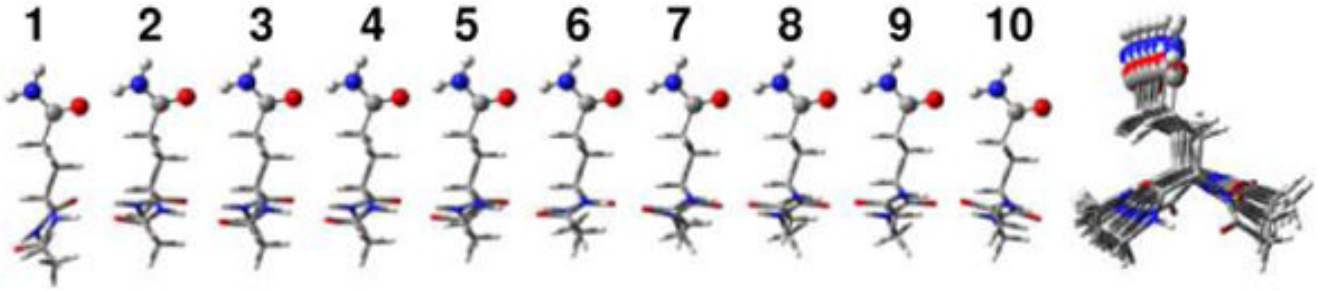

Figure 2.
Structure of the (acetyl-Q-$NHCH_3)_{10}$ parallel β-sheet. The left view is perpendicular and right view coaxial to the amidic H-bonds. The amides of the Q's are shown as balls and sticks.

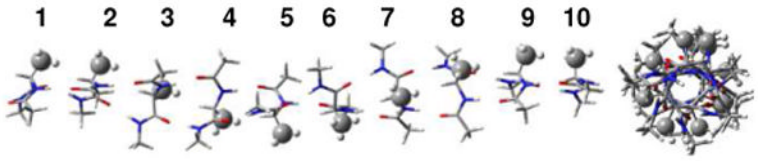

Figure 3.
Structure of the (acetyl-A-$NHCH_3$)$_{10}$ parallel β-sheet. The view on the right is perpendicular to that on the left. Note the helical sheet. The methyls are represented as ball and sticks.

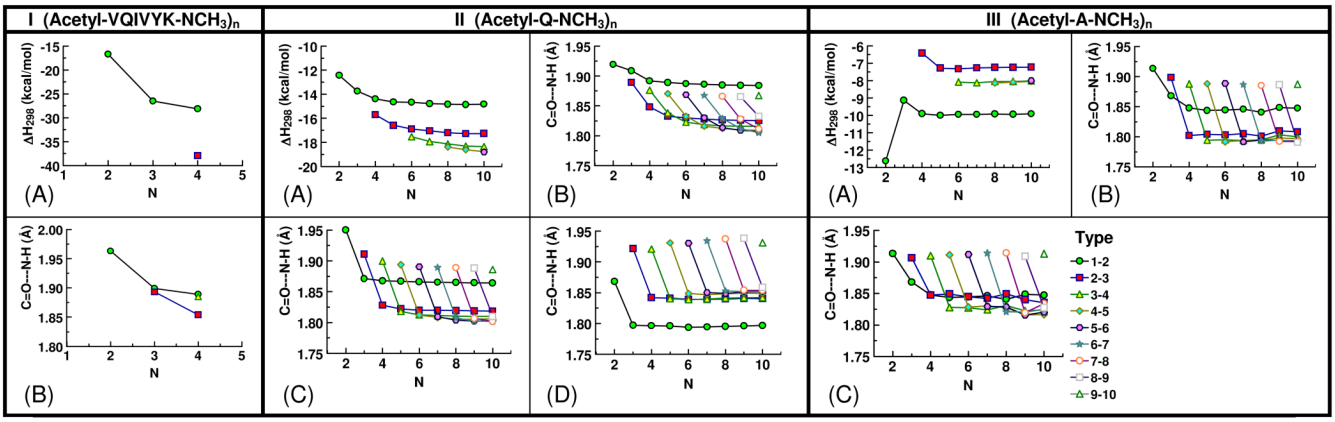

Figure 4.

I (acetyl-VQIVYK-NHCH$_3$)$_N$ (A) Interaction enthalpies, (B) H-bond lengths between the side chains of Q. **II (acetyl-Q-NHCH$_3$)$_N$** (A) Interaction enthalpies, (B) H-bond lengths between the side chains of Q, (C) Backbone H-bonds near the c- and (D) n-termini. **III (acetyl-A-NHCH$_3$)$_N$** (A) Interaction enthalpies, backbone H-bonds near the (B) c- and (C) n termini. An interaction "type" refers to that between strands N and N-1