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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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Amyloid fibrils formed from the tau protein are a symptom and probable cause of Alzheimer's disease.[1−3] Mutation studies have shown that the six amino acid sequence ^{306}VQIVYK^{311} is essential for the formation of these fibrils.[4,5] Recent crystallographic studies of VQIVYK peptides have shown 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 protein. Similar crystals have been formed from other small peptides believed to be essential for formation of other amyloid structures.[6−8]

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 under the right circumstances. Both experimental[9,10] and theoretical[11] evidence indicates that polyalanine and other α-helical peptides owe their stability to cooperative enthalpic interactions. Furthermore, chains of formamides[12] can achieve stabilization enthalpies of ∼13 kcal/mol, while those of the more polarizable 4-pyridone[13] can achieve stabilizations of 23 kcal/mol.

Molecular orbital (MO) studies of antiparallel β-sheets of polyglycine models have shown the H-bond cooperativity to be negated by the 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; this amide 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] suites of programs, using the ONIOM[18] method with B3LYP/D95(d,p) and semiempirical MO AM1[19] as the high- and low-level methods, respectively. We used GAUSSIAN 09 with the GAUSSIAN 03 version of AM1. The entire peptide backbone and the Q side chains (containing the amide groups) constituted the high-level portion, and the side chains of the other residues composed the low-level portion. The methods are analogous to those previously employed for α-helices.[11] We used single-point counterpoise (CP) corrections on the high-level portion of the fully optimized β-sheets to correct the energies for basis-set superposition error, as the structures are too large for the CP optimization procedure.[20] As the CP and vibrational corrections to the enthalpies remained 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 was done for chains of formamides[12] and 4-pyridones.[13]

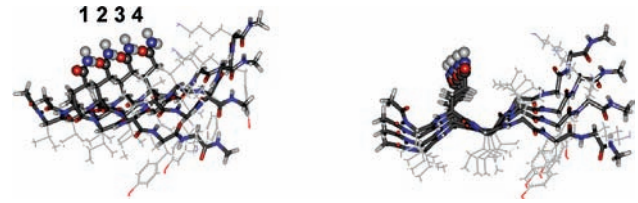

Figure 1. Structure of the (acetyl-VQIVYK-$NHCH_3$)$_4$ parallel β-sheet. The right view is coaxial with the H-bonds between Q side chains. The amides of the Q side chains are shown as balls and sticks, the backbones as tubes, and the other (non-Q) side chains as wireframes.

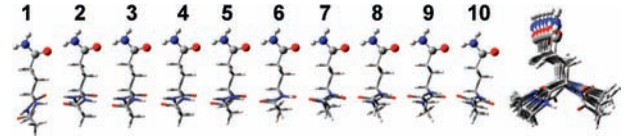

Figure 2. Structure of the (acetyl-Q-$NHCH_3$)$_{10}$ parallel β-sheet. The left view is perpendicular and the right view coaxial to the amidic H-bonds. The amides of the Q's are shown as balls and sticks.

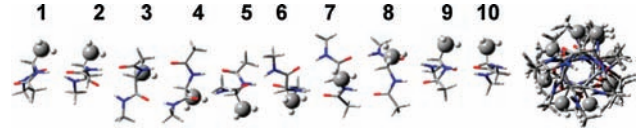

Figure 3. Structure of the (acetyl-A-$NHCH_3$)$_{10}$ parallel β-sheet. The view on the right is perpendicular to that on the left. The helical sheet should be noted. The methyls are represented as balls and sticks.

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-$NHCH_3$ (A = alanine) (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, respectively. These smaller models also allowed us to calculate sheets containing more strands.

As shown in 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 Q's become shorter

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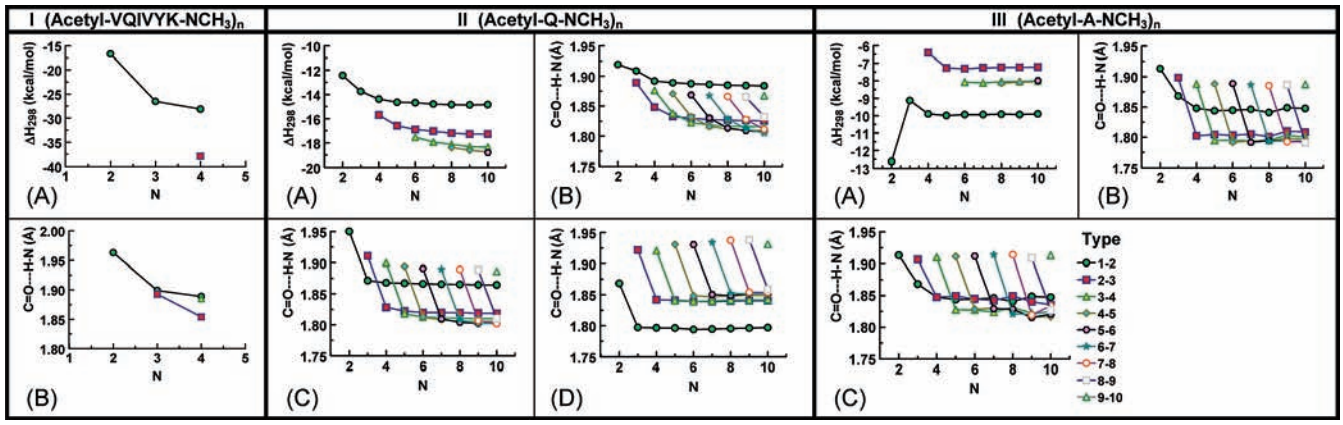

Figure 4. (I) Results for (acetyl-VQIVYK-$NHCH_3)_N$: (A) interaction enthalpies; (B) lengths of H-bonds between Q side chains. (II) Results for (acetyl-Q-$NHCH_3)_N$: (A) interaction enthalpies; (B) lengths of H-bonds between Q side chains; (C, D) lengths of backbone H-bonds near the (C) C- and (D) N-termini. (III) Results for (acetyl-A-$NHCH_3)_N$: (A) interaction enthalpies; (B, C) lengths of backbone H-bonds near the (B) C- and (C) N-termini. An interaction "type" refers to that between strands N and $N - 1$.

(especially near the center of the H-bonding chains) as the number of strands 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, while 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 because improving one interaction usually leads to the degradation of others. We call this phenomenon attractive strain, as all of the interactions are attractive yet cannot be simultaneously optimized.[21] Attractive strain was also observed for VQIVYK sheets (see the Supporting Information), as there are a total of eight 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) because of the difference between the two H-bonds connecting each pair of strands (as manifested by the different O···H distances). From the foregoing, one can infer the importance of the Q−Q side-chain interactions in maintaining the relatively flat backbones of the VQIVYK sheets.

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

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Supporting Information Available: Complete refs 16 and 17, interaction enthalpies, Cartesian coordinates, and pictures of structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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