Cooperative Hydrogen-Bonding in Models of Antiparallel β-Sheets

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We present fully geometrically optimized density functional theory calculations at the B3LYP/D95(d,p) level on antiparallel β-sheet models consisting of two or four strands of two or four glycine residues and artificial nylon-like two- or four-strand models of two glycine residues separated by two methylene groups. Unlike the H-bonds in α-helices and chains of H-bonding amides, the association of polyglycine strands shows little or no H-bond cooperativity. We show that C_5 *intra*strand H-bonds are either disrupted or enhanced upon formation of *inter*strand H-bonds, depending upon the H-bonding pattern in the glycine (but not the nylon-like) structures. The apparent relative absence of H-bond cooperativity in β-sheet models of polyglycine derives from the weakening and strengthening of these *intra*strand H-bonds. Normal cooperative H-bonding occurs when the nylon-like strands (which cannot form the *intra*strand H-bond) form two- and four-strand sheets. The H-bonding interactions are stronger and the H-bonding distances shorter (on average) than previously reported for similar calculations on α-helical structures, consistent with the observations that amyloid diseases, such as Alzheimer's and prion diseases, involve conversion of α-helical secondary structures to (presumably more stable) β-sheets.

Introduction

Many recent reports of both experimental[1−3] and theoretical studies[4−14] have demonstrated the extensive H-bond cooperativity of chains of amidic H-bonds. These cooperative effects have been confirmed in helical peptides. However, despite the reports of H-bonding cooperativity in modeling studies,[15] recently reported density functional theory (DFT) calculations failed to provide evidence for cooperativity along the H-bonding chains in β-sheets.[16] Wu has reported cooperativity in both α- and 3_{10}-helices[9] and in sheets of (unnatural) β-polyglycines[12] but little or none in β-sheets of the natural α-polyglycines.[16]

In this paper, we shall examine the H-bonds in several fully optimized models of antiparallel β-sheets to understand the lack of cooperativity of the H-bonds in these structures and attempt to elucidate the reasons that may not be readily apparent from a simple comparison of H-bonding energies between individual β-strands. The relative strengths and cooperative natures of β-sheets and α-helices are of particular interest as conversion from α-helical to β-sheet secondary structures has been associated with amyloid diseases,[17] such as Alzheimer's, and prion diseases, such as Creutzfeldt-Jakob.[18,19]

We shall consider H-bonded antiparallel β-sheets formed from three different peptide strands: (1) a structure with two glycine residues, GLY2, (2) a structure with four glycine residues, GLY4, and (3) a nylon-like structure with two glycine residues where a $-CH_2-CH_2-$ spacer has been added between the two residues in order to prevent intrastrand (C_5) H-bonds, GLY2C. In each case, we replaced the terminal COOH with CHO. We consider the different dimeric and tetrameric H-bonded antiparallel β-sheet structures that can be formed which preserve both a plane and a center of symmetry (for ease of optimization).

Methods

DFT calculations were performed using the Gaussian 98 suite of computer programs[20] on our cluster of Pentium 3, Pentium 4, and AMD Athlon computers which are parallelized using Linda.[21] All calculations used the D95(d,p) basis set and the B3LYP functional. This method combines Becke's 3-parameter functional[22] with the nonlocal correlation provided by the correlation functional of Lee, Yang, and Parr.[23] The geometries of all species were completely optimized with the following constraints: (1) a plane of symmetry (C_s) containing all the C's, N's, O's, and amidic H's was imposed upon each of the individual β-strands; (2) in addition, each of the two- and four-strand species was also constrained to contain a center of symmetry (C_{2H}). The vibrational frequencies were calculated for the planar structures, using the normal harmonic approximations employed in the Gaussian 98 program, to verify the stationary points and calculate the enthalpies of the various species. All frequencies were real except for some very low frequency imaginary vibrations that involve out of plane rocking motions of the CH_2 groups in some (but not all) structures. The single-point a postieri counterpoise (CP) corrections were calculated using the procedure incorporated in Gaussian 98. Optimization on the CP-corrected potential energy surfaces (CP-OPT)[24] was not completed due to the excessive CPU time required.

Results and Discussion

To facilitate the presentation, we shall begin with the single strands and then proceed to the two- and four-stranded sheet structures. The single-strand structures are referred to as GLY2, GLY4, and GLY2C2, to indicate the type of peptide unit that makes up a single strand. The two-stranded sheet structures are named by using a prefix 2, followed by the name of the peptide units in the middle, and a suffix of S or L to designate the size

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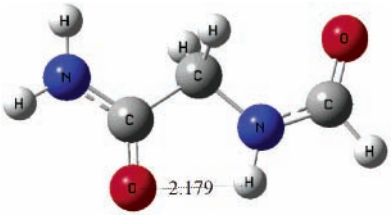

Figure 1. GLY2.

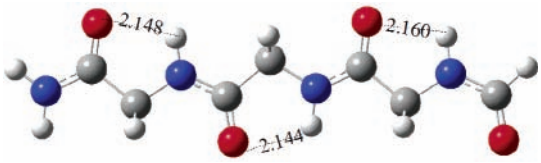

Figure 2. GLY4.

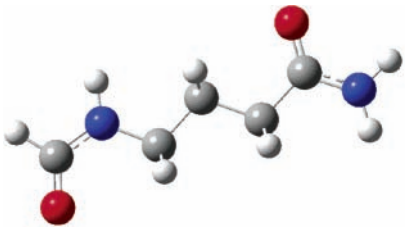

Figure 3. GLY2C.

of the H-bonded ring as small or large. A similar nomenclature is used to name the four-stranded sheet structures with the numeral 4 used as the prefix. Thus, the two-stranded structures are referred to as 2GLY2S, 2GLY2L, 2GLY4S, 2GLY4L, 2GLY2CS, and 2GLY2CL. The four-stranded structures are referred to as 4GLY2S, 4GLY2L, 4GLY4S, 4GLY4L, 4GLY2CS, and 4GLY2CL. We shall use the suffixes S (small) and L (large) to signify the size of the central interstrand H-bonded ring in the four-stranded sheets.

Single Strands. The single strands of GLY2 and GLY4 have planar optimized geometries as confirmed by the lack of any imaginary vibrational frequencies. The structure of GLY2 is illustrated in Figure 1. Planar β-strands of this type have a weak internal H-bond which is often referred to as a C_5 interaction (denoting a cyclic H-bonding structure containing five atoms). The O···H distance is a relatively long 2.179 Å, while the N−H···O angle of 107.2° is not at all optimal for a H-bond. Figure 2 depicts the structure of GLY4. This structure contains three C_5 H-bonding interactions. The O···H distances are all smaller than in GLY2, while the central O···H distance is the smallest of the three. Both the shorter O···H distances and pattern of the shortest H-bond in the center are qualitatively reminiscent of the H-bond distances in cooperative H-bonding chains.[6,25]

To study the effects of these intrastrand (C_5) H-bonding interactions within single β-strands upon the energetics of H-bonding between the strands to form β-sheets, we designed a related strand that cannot attain the C_5 H-bonding interaction, GLY2C (Figure 3). This strand resembles a nylon-2 structure (three CH_2 units between the amide functions). It can also be characterized as a model for a γ-amino acid strand. In this structure (as well as in all sheets made from it), the central C−C−C is constrained to be coplanar with the other heavy atoms (C, N, O). This planar structure is not a minimum as it has two imaginary vibrational frequencies.

Two-Stranded Sheets. The β-strand GLY2 can form two different centrosymmetric two-stranded β-sheets, 2GLY2S and 2GLY2L, which are illustrated in Figures 4 and 5.

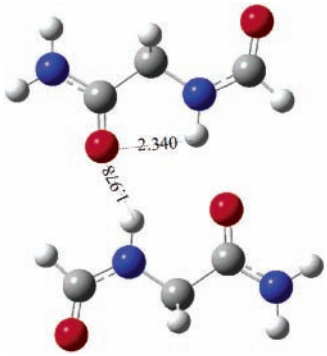

Figure 4. 2GLY2S.

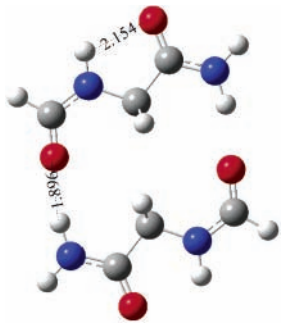

Figure 5. 2GLY2L.

TABLE 1: Interaction Enthalpies (kcal/mol) and Number of H-Bonding Interactions of Each Type for the Two- and Four-Stranded Species[a]

			number of H bonds	
species	ΔH_{int}	cooperativity	interstrand	intrastrand (C_5)
2GLY2S	−4.85		2	0
2GLY2L	−13.99		2	2
4GLY2S	−36.74	3.91	6	2
4GLY2L	−27.13	3.44	6	0
2GLY4S	−22.91		4	4
2GLY4L	−12.96		4	2
4GLY4L	−58.98	0.20	12	4
4GLY4S	−46.37	−2.46	12	2
2GLY2CS	−7.38		2	0
2GLY2CL	−9.18		2	0
4GLY2CS	−32.35	6.61	6	0
4GLY2CL	−31.19	7.25	6	0

[a] Only peripheral intrastrand (C_5) interactions are counted as the interior ones are weakened or broken (see the text).

Vibrational calculations confirmed both of these structures to be minima. From Table 1, one can see that the H-bonding enthalpy of 2GLY2L (−13.99 kcal/mol) is significantly more negative than that of 2GLY2S (−4.85 kcal/mol) despite the fact that they each have two very similar amidic H-bonds between the two strands. Wu has previously reported similar behavior in two-stranded β-sheets of polyglycine. He suggested that the differences in the stabilities of the small and large rings might be attributed to secondary electrostatic interactions such as those discussed by Jorgensen for guanine−cytosine complexes.[26] However, this seems to us an unlikely explanation as its general validity has been questioned by Leszczynski,[27]and we have recently shown the individual H-bonds in the guanine−cytosine complex to be cooperative,[28] in disagreement with expectations from unique consideration of the secondary electrostatic effect. Furthermore, the roughly 9 kcal/mol difference in interaction energies (greater than the interaction energies of all but the strongest H-bonds) seems much too large to come from secondary electrostatic interactions.

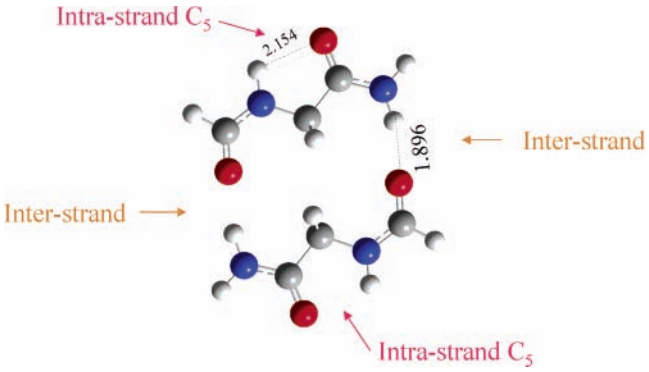

Figure 6. Cyclic cooperative H-bonding interactions in 2GLY2L.

Wu also suggested that *inter*strand C−H···O H-bonding interactions might contribute to the differences between the small and large ring interactions. However, the H···O distances (2.855 Å) that he reported for the antiparallel β-sheet seem much too long for such H-bonds. Furthermore, their contributions would be small (<1 kcal/mol) should they exist. Consequently, we looked elsewhere for a suitable explanation.

Comparison of the C_5 H-bonding distances in Figures 4 and 5 to that of Figure 1 shows that the C_5 O···H interaction (2.179 Å in GLY2) has expanded to 2.340 Å in 2GLY2S and contracted to 2.154 Å in 2GLY2L. Previous theoretical calculations on formamide chains[6,25] have shown that cooperative H-bonds decrease the O···H distances as they increase the stability of the interactions. We can, therefore, use the C_5 H-bond distances as an indication of the strengthening or weakening of these interactions. We shall refer to the C_5 interactions as *internal* if they are part of an interstrand H-bond ring; otherwise we shall call them *peripheral*. The C_5 interactions are both internal, and thus weakened, in 2GLY2S but peripheral, and thus enhanced, in 2GLY2L relative to that in a single-stranded structure. We suspected that the weakening of C_5 interactions could also lead to the decreased stability of 2GLY2S when compared to 2GLY2L. This difference in stability is also exhibited in the significantly different interstrand H-bonding distances in 2GLY2S (1.978 Å) and 2GLY2L (1.896 Å) (Figures 4 and 5). The shorter distances in 2GLY2L also correlate with the more negative interstrand interaction enthalpy. In fact, the structure of 2GLY2L is consistent with four *cooperative* H-bonds (two between the strands and two C_5) within a cyclic structure (see Figure 6). On the other hand, the structure of 2GLY2S shows no cooperative interaction as it has weakened C_5 internal H-bonding interactions which have O···H distances that increased upon formation of the dimer. Thus, the enhanced stability of larger H-bonded rings appears to be primarily due to the strengthening of C_5 H-bonded interactions within each strand and the resulting cooperative interactions.

To test this hypothesis, we examined the two centrosymmetric two-stranded structures that can be constructed from GLY2C: 2GLY2CS and 2GLY2CL (see Figures 7 and 8). Since the intrastrand (C_5) interactions are impossible in these structures, we can estimate the effect of the C_5 interactions from the differences in the H-bonding energies between the dimers of GLY2 and GLY2C. One should note another difference between the two forms of each dimeric structure: 2GLY2L and 2GLY2CL have interstrand H-bonds between C═O's and N−H's that are in terminal positions of each strand, while 2GLY2S and 2GLY2CS do not. These structures have two imaginary vibrational frequencies, two pairs (symmetric and antisymmetric) which correspond to out of plane CH_2 deformations. As can be seen from Table 1, 2GLY2CL has a stronger

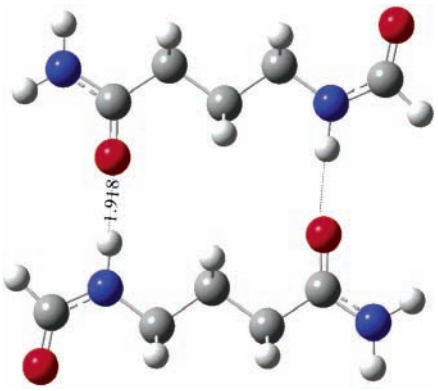

Figure 7. 2GLY2CS.

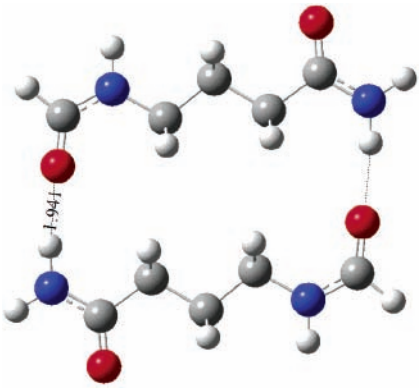

Figure 8. 2GLY2CL.

H-bonding enthalpy (−9.18 kcal/mol) than 2GLY2CS (−7.38 kcal/mol), but the difference between the two (1.80 kcal/mol) is significantly less than that between the dimers of GLY2 (9.14 kcal/mol). This smaller difference could be due (at least partially) to secondary electrostatic interactions. The shorter O···H distances calculated for the less stable 2CLY2CL are not consistent with the expectation that shorter H-bonding distances correlate with stronger H-bonds. The reason for this, while not immediately apparent, is consistent with secondary electrostatic interactions. However, the amides involved in the H-bonds show considerably more delocalization in 2GLY2CL (which has the stronger H-bonds) than in 2GLY2CS. The C−N and C═O bond lengths are 1.352 and 1.232 Å in 2GLY2CL and 1.367 and 1.231 Å in 2GLY2CS, respectively. We suggest that the small energetic differences between the two dimers of GLY2C are mostly due to the differences in the H-bonds between terminal and nonterminal C═O's and N−H's, with a possible contribution from secondary electrostatic interactions.

Let us now consider the centrosymmetric dimers of GLY4. Once again there are two, 2GLY4L and 2GLY4S (see Figures 9 and 10). Unlike 2GLY2S and 2GLY2L, these two planar structures are not minima as three (of the four) CH_2 out of plane deformations have small imaginary vibrational frequencies for each of the two structures. Here, the H-bonding patterns become more complex as 2GLY4L contains two small H-bonding rings and one large, while 2GLY4S contains one small and two large rings (as those in 2GLY2S and 2GLY2L, respectively). 2GLY4S is more stable by 9.61 kcal/mol, which is roughly consistent with the energy difference between 2GLY2S and 2GLY2L which also differ by the exchange of a small for a large ring. We first consider the H-bonds between the strands. In 2GLY4L, the outer two H-bonds participate in only small rings, while the inner two are part of both small and large rings. In 2GLY4S, the situation is reversed: The outer two H-bonds participate

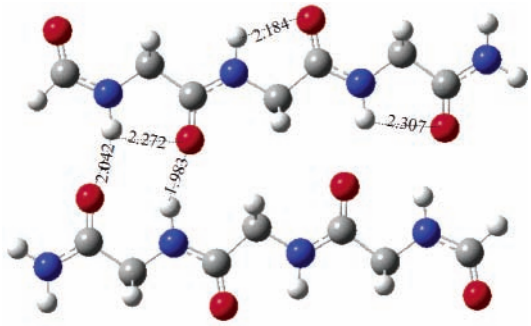

Figure 9. 2GLY4L.

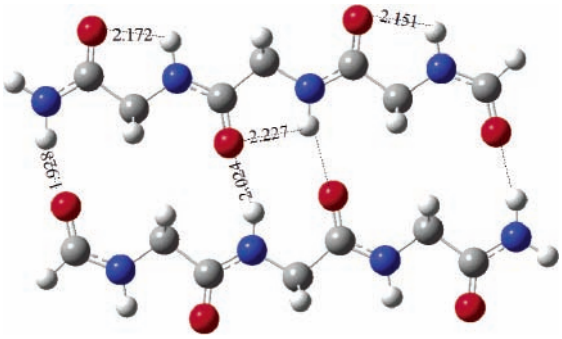

Figure 10. 2GLY4S.

only in large rings, while the inner two participate in both large and small rings. Of the three C_5 interactions that exist in each GLY4 single strand, four (two in each strand) remain peripheral for 2GLY4S, but only two in 2GLY4L. Of the peripheral C_5 interactions, the O···H distance of the one nearest the C═O end of the strand is shortened by 0.009 Å and the other is lengthened by 0.024 Å in 2GLY4S, while that in 2GLY4L is lengthened by 0.040 Å. The other, internal, C_5 interactions are hindered by the formation of interstrand H-bond rings. Their O···H distances lengthen by 0.159 and 0.112 Å for 2GYL4L and by 0.083 Å for 2GLY4S compared to the single strands. The more stable isomer, 2GLY4S, has two large and one small ring with interstrand and C_5 H-bond distances averaging 1.976 and 2.183 Å, respectively, while the less stable 2GLY4L contains two small and one large ring with longer interstrand and C_5 H-bond distances of 2.012 and 2.254 Å. Thus, similar to the two-stranded β-sheet structures of GLY2 peptides, the structure with the greater number of large H-bonded rings, shorter C_5 H-bond distances, and shorter interstrand H-bond distances is observed to be energetically favored for the sheet structures of the GLY4 peptides.

Four-Stranded Sheets. One can imagine two different centrosymmetric structures for four-stranded sheets of each of the three kinds of strands. In one, a small H-bonding ring exists between the two central strands (or for those made from GLY4's, the most central ring), while large H-bonding rings connect the other two strands to the central pair. In the other structure, the positions of the small and large rings are reversed (large between the central strands and small for the two other interstrand interactions). We shall continue to use the suffix S or L here to indicate the size of the central H-bonding ring. These structures constructed with GLY2's are illustrated in Figures 11 and 12, with GLY2C's in Figures 13 and 14 and with GLY4's in Figures 15 and 16. Unlike the analogous two-stranded structures, each of the four-stranded GLY2 structures has two imaginary frequencies that involve CH_2 out of plane deformations of only the exterior CH_2's. The inner CH_2's do not participate in these imaginary vibrations. On the other hand,

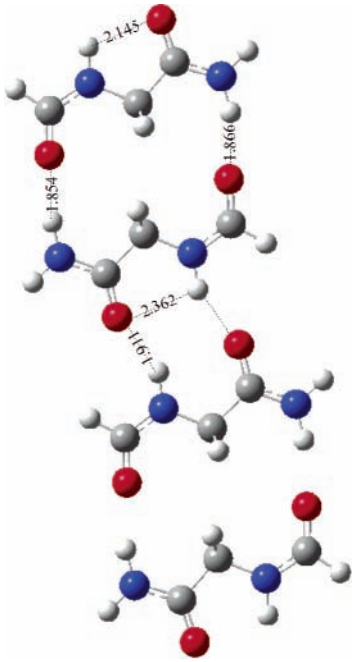

Figure 11. 4GLY2S.

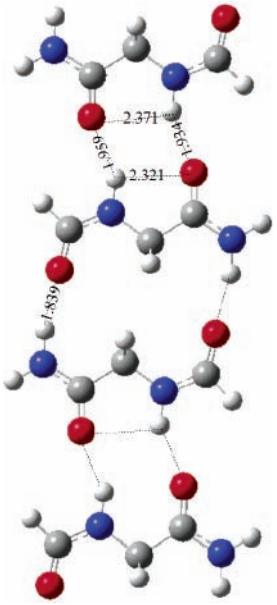

Figure 12. 4GLY2L.

the four-stranded structures derived from the GLY4's have imaginary frequencies that correspond to out of plane deformations of all the CH_2's in four (4GLY4L) or seven (4GLY4S) of the eight appropriate symmetry combinations.

The differences in the total interaction energies (relative to four appropriate single strands) between 4GLY2S and 4GLY2L is 9.61 kcal/mol, while that between 4GLY4S and 4GLY4L is 12.61 kcal/mol. Once again, the more stable of each of these pairs of isomeric structures contains one more large ring and one fewer small ring than the less stable one.

Of the structures that have been considered so far, these are the first that contain chains of amidic H-bonds (as opposed to chains of C_5 H-bonds found in GLY4). In each of the two structures, there are two such chains, each containing three H-bonds. From previous reports,[4,7,13,25] we expect the central O···H distance in each chain to be the shortest, and thus (presumably) the strongest. Simple inspection of the interstrand

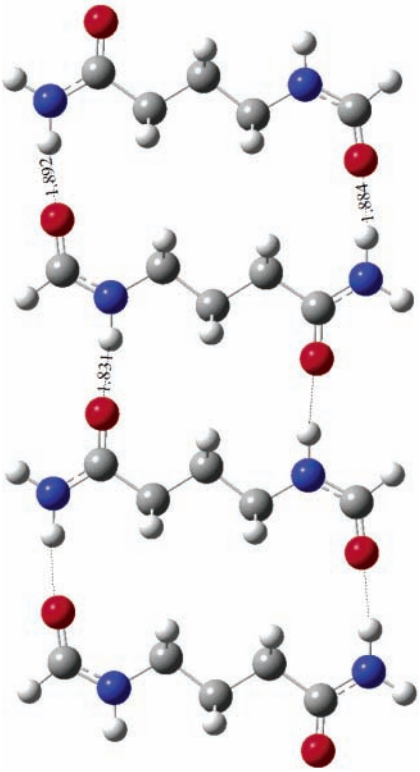

Figure 13. 4GLY2CS.

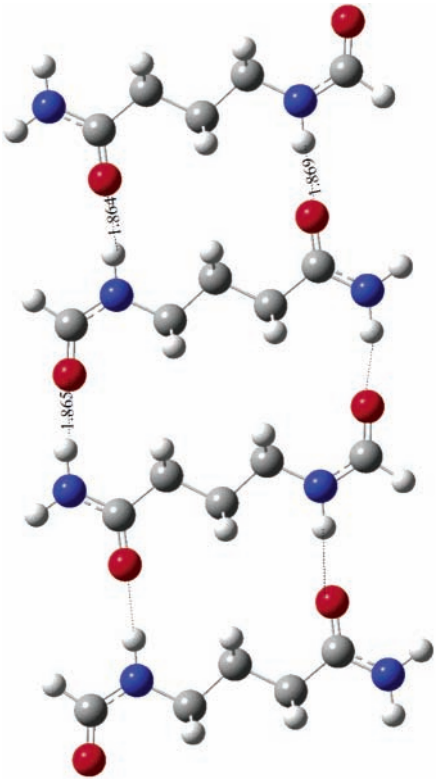

Figure 14. 4GLY2CL.

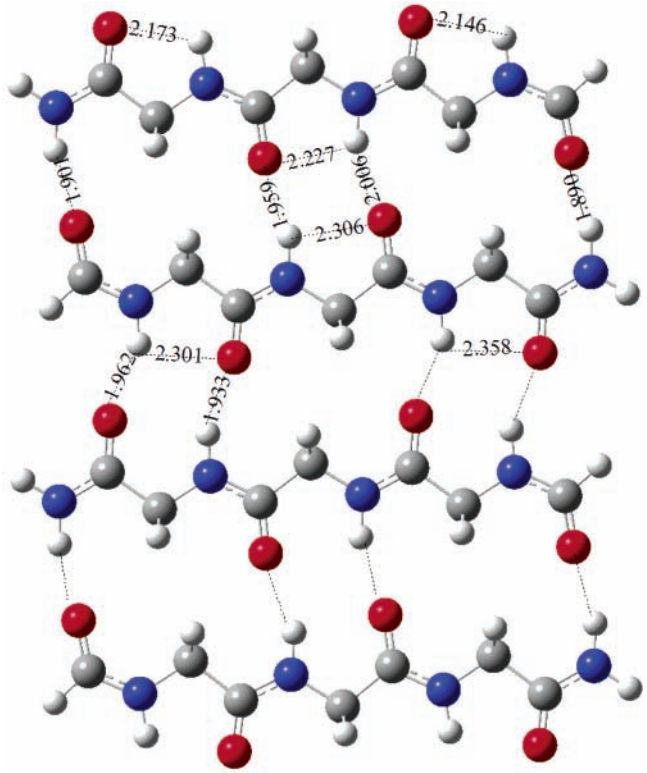

Figure 15. 4GLY4L.

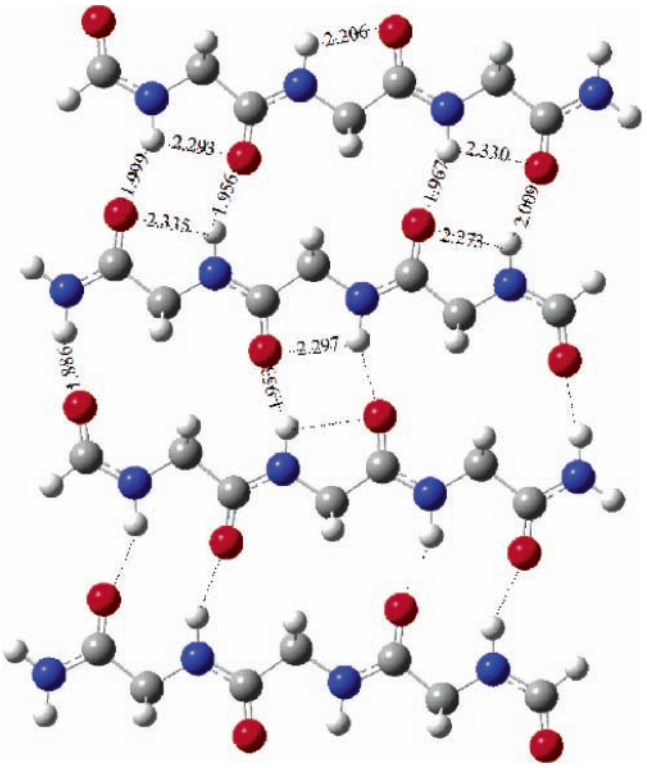

Figure 16. 4GLY4S.

H-bonds in Figure 11 does not immediately confirm this expectation, as the central pair of interstrand H-bonds for 4GLY2S are longer than those between the outer strands and the central pair. However, comparison with the two-stranded structures (2GLY2S and 2GLY2L) indicates that each of the comparable H-bonds is shorter in the quadruple-stranded structures. For example, from Figures 11, 4, and 5, we see that the central interstrand H-bonds in 4GLY2S (1.911 Å) are shorter than those in 2GLY2S (1.978 Å) and the other interstrand H-bonds (1.854 and 1.866 Å) are shorter than those of 2GLY2L (1.986 Å). Figure 11 shows that for 4GLY2L, the central interstrand H-bond (1.839 Å) is shorter than that in 2GLY2L (1.896 Å) while the other H-bonds (1.959 and 1.934 Å) are shorter than those of 2GLY2S (1.978 Å). The C_5 H-bonds (all internal in 4GLY2L) have increased in length, while in 4GLY2S the two peripheral C_5 H-bonds have slightly shortened and the

two internal H-bonds have lengthened. Thus, while the peripheral C_5 H-bonds show cooperative strengthening in 4GLY2S, those in the interior weaken as the traditional (interstrand) H-bonds become stronger. One can imagine a single cyclic chain of H-bonds containing the six interstrand and two peripheral C_5 interactions for this structure, but not for 4GLY2L.

For the H-bonding tetramers of GLY2C, similar patterns obtain for the amidic interstrand H-bond lengths. The H-bonds of each type (small or large ring) between each pair of adjacent strands are shorter than similar H-bonds between the H-bonding dimers. Thus, the O···H distances in the 2GLY2CS structure (1.918 Å) become 1.831 Å in the central small ring of 4GLYC2S (Figure 13) and 1.864 and 1.869 Å in the outer small rings of 4GLY2CL (Figure 14), while those in the 2GLY2CL structure (1.941 Å) become 1.892 and 1.884 Å in the outer rings of 4GLY2CS (Figure 13) and 1.865 in the inner ring of 4GLY2CL (Figure 14).

The variations in the C_5 H-bonding interactions in 4GLY4S and 4GLY4L require a somewhat more complex discussion. Let us first consider 4GLY4L (Figure 15). There are two peripheral C_5 H-bonding interactions on each end of the sheet. The one nearer the C═O end has shortened going from GLY4 to 2GLY4S (Figure 10) to 4GLY4L from 2.160 to 2.151 to 2.146 Å. However, the other one has lengthened from 2.148 to 2.172 to 2.173 Å (no significant change on going from two 2GLY4S's to 4GLY4L). The increased C_5 O···H distance upon formation of 2GLY4S from two GLY4's is apparently due to the weakening of the cooperative interactions within the strand as the central C_5 interaction lengthened from 2.144 Å in GLY4 to 2.227 Å in 2GLY4S. This suggests that the intrastrand cooperativity has a larger effect upon this C_5 interaction in GLY4 than the interstrand interaction in 2GLY4S. Also, extending the interstrand H-bonding chain to three H-bonds increases the effect of their cooperativity upon this C_5 H-bond. The C_5 interaction distances in each strand that are involved in the small ring between the outer strands are 2.227 Å for that in the outer strand and 2.306 Å for the inner strand. The analogous interaction in 2GLY4S (Figure 10) is 2.227 Å (the same as that of the outer strand in 4GLY4L). However, the C_5 interaction distances in the two small rings that connect the central strands are significantly longer (2.301 and 2.358 Å).

For 4GLY4S (Figure 16), all of the C_5 interaction distances are appreciably longer than in GLY4. The peripheral ones (2.206 Å) are even longer than that in the completely isolated C_5 interaction of GLY2 (2.179 Å). The C_5 interaction distances that are involved in the small rings that connect the strands are similar to each other (2.273−2.335 Å).

Cooperativity. We determined the cooperativity of the interstrand interactions by subtracting the appropriate interstrand enthalpies of interaction for each of the three sets of two-stranded structures from that of the four-stranded structure. Thus, the cooperativity in 4GLY2S would be −36.74 less −4.85 and twice −13.99 or 3.91 kcal/mol, if we express the cooperativity as a positive quantity. Despite the observation that the central H-bond in each H-bonding chain is shorter (and therefore presumably stronger) than the comparable H-bond in the appropriate dimer, the energetic data (Table 1) indicate little cooperativity in the tetramers of GLY2 and virtually none at all (even negative cooperativity in 4GLY4L) in the tetramers of GLY4. However, the tetramers of GLY2C exhibit a significant cooperative effect. The two new H-bonds in tetramers formed from two dimers provide almost twice the stabilization as the comparable pair of H-bonds in a dimer formed from two monomers. For example, the cooperative contributions to the two four-stranded structures of GLY2C are 7.25 and 6.61 kcal/mol while the H-bonding energies for the two-stranded structures are −9.18 and −7.38 kcal/mol (see Table 1). The interactions between the pairs of two-stranded structures are 13.99 kcal/mol to form 4GLY2CS and 16.43 kcal/mol to form 4GLY2CL.

The apparently small and negative cooperativities seen for the two four-stranded structures of GLY4 (4GLY4L and 4GLY4S) are due to the weakening of the C_5 interactions that occur with interstrand H-bonding. Inspection of Figures 15 and 16 and Table 1 will show that of the 12 C_5 internal H-bonds in the four isolated strands (3 in each) 4GLY4L has 4 remaining peripheral C_5 H-bonding interactions, while 4GLY4S has only 2. We have seen from the discussion above that the internal C_5 interactions are weakened (as indicated by an increase in bond lengths) while the peripheral ones are generally strengthened or only very slightly weakened. When 4GLY4L is compared to the three two-stranded interactions contained within it, there is a difference of 6 peripheral C_5 H-bonds (each of the two 2GLY4S's has 4 peripheral interactions and the 2GLY4L has 2 peripheral interactions compared to a total of 4 peripheral interactions in 4GLY4L).

Similarly, 4GLY4S contains 6 fewer peripheral interactions than the 3 analogous two-stranded interactions that it contains. Furthermore, the remaining two peripheral C_5 O···H distances in 4GLY4S increase slightly, which indicates that they are weakened. The cooperativity that might be observed due to the formation of additional interstrand H-bonds is diminished by the loss of some C_5 H-bond interactions and the weakening of others.

All the pairs of isomeric structures constructed from GLY2S or L and GLY4S or L (but not GLY2CS or L) differ in interaction enthalpies by about 9−10 kcal/mol if one subtracts the cooperative part of the interaction. The 12.61 kcal/mol difference between the interaction enthalpies of 4GLY4S and L becomes 8.95 kcal/mol after subtraction of the cooperative interactions, while that between 4GLY2S and L becomes 9.14 kcal/mol (see Table 1). This observation reflects the H-bonding motifs in that the more stable of each isomeric pair of structures has one more large and one fewer small H-bonding ring.

For the cases that we present in this paper, we cannot assign enthalpies to individual H-bonds (except for those in 2GLY2CS and 2GLY2CL, which have pairs of equivalent H-bonds). However, since H-bond length has been correlated with enthalpies, we investigated the average interstrand H-bond enthalpy as a function of the average H-bond length. The average enthalpies have been calculated by dividing the interaction enthalpy by the total number of H-bonds (interstrand and C_5). The average enthalpies for the sheet structures of GLY2 and GLY4 are plotted in three different ways in Figure 17: versus the average interstrand distance, the average intrastrand (C_5) distance, and the average of all (inter- and intrastrand) H-bond distances. Though all three average H-bond distances correlate with the average H-bond enthalpies, the correlation with the interstrand H-bond distances is best.

As noted above, Wu has reported calculations similar to those reported here. His calculations differ from ours in that he used HF/6-31G* instead of B3LYP/D95** and the geometries are not fully optimized. As all strands were constrained to have the same geometry, the differences in the C_5 interactions could not become apparent. The interstrand H-bond distances that he reported (2.150 Å) are significantly longer than those reported here.[16] Comparison of H-bonding distances in water dimer[29] calculated by different methods indicates that HF calculations tend to overestimate H-bonding distances as compared to DFT

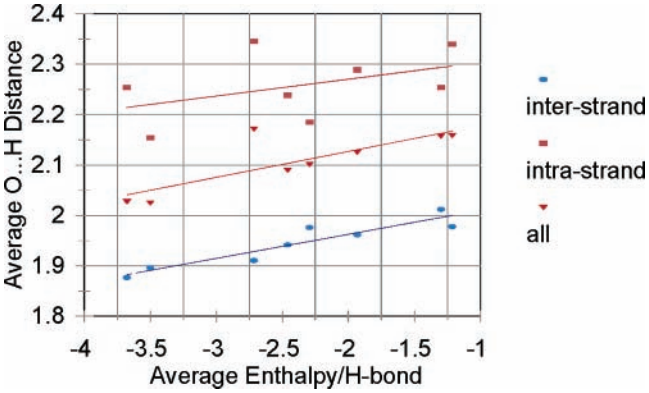

Figure 17. Average H-bond enthalpy vs average O···H distance for all H-bonds, only the interstrand H-bonds, or only the intrastrand H-bonds for all dimers and tetramers of GLY2 and GLY4.

and MP2. We have observed a similar trend in H-bonding formamide chains.[25] We also note that Wu reports interaction energies without correction for basis-set superposition error (BSSE). Our results are reported as enthalpies at 298 K, after correction for BSSE and vibrations. Had he applied these corrections, all his reported interactions would have been smaller in magnitude. Wu's reports of significant cooperativity in sheets of β-glycine[12] (where C_5 H-bonding interactions cannot occur) are qualitatively consistent with our calculations on the dimeric and tetrameric sheets formed from 2GLY2C, which could be characterized as a nylon-2 or γ-glycine-like structure. However, strands of β-glycine have all the C═O's essentially parallel, while the C═O's in strands of both α-glycine (the natural amino acid) and γ-glycine (nylon-2) are antiparallel. Wu also reported significant cooperativity for H-bonding chains of acetamide. However, the amount of cooperativity he reports for strands that consist of acetyl$(Gly)_2NH_2$ is negligible as the reported incremental binding energy for forming a hexameric sheet is only 0.8 kcal/mol (or 6%) greater than that for forming a dimeric sheet (from Table S3 of the Supporting Information).[16]

The sheets formed from 2GLY2C's are analogous to nylon structures, some of which have been treated theoretically.[30] Nylon-like structures have been used in self-assembled nanomaterials.[31−33] Obvious parallels between nylon and peptide sheetlike structures exist. However, the absence of the C_5 internal H-bonds in the nylon sheets implies that the H-bonding between strands should be significantly more cooperative (and thus stronger) than in β-sheets of polyglycine.

General Discussion

H-Bonding distances have been reported to be generally about 0.1 Å shorter in β-sheets than in α-helices.[34,35] Comparisons with our recent fully optimized calculations on several α-helical peptides[4,13] agree with these reports. Based upon these differences in H-bond distances, the interstrand H-bonds in the β sheets should be generally stronger than those in the α-helices. This is best illustrated by comparing the interactions in the GLY2C series with those in the α-helices. The enthalpy of interaction between pairs of GLY2C's is either −9.18 or −7.38 kcal/mol depending upon whether the dimeric structure is 2GLY2CL or 2GLY2CS. As two H-bonds exist in each of the dimeric structures, we can take the individual H-bond enthalpies as half of these values (−4.59 or −3.69 kcal/mol). Both of these values are larger than the average H-bonding energy for α-helical acetyl$(Ala)_{17}NH_2$, taken as the energy difference between the α-helical and extended β-strand forms divided by 15 (the number of H-bonds), which comes to $-31.4/15 = -2.1$ kcal/mol.[4] This comparison needs to be qualified as (1) we are comparing enthalpy differences in the β-sheets with energy differences in the helices and (2) the model amino acid is glycine in the sheets but alanine in the helices. The differences in enthalpy of the sheets should parallel those in energy of the helices if the vibrational corrections for forming sequential H-bonds in the helices are small. This energy is 0.78 kcal/mol (0.34/H-bond) for the formation of the 3_{10}-helix of acetyl$(Gly)_5$-NH_2 from the extended β-strand.[5] On the other hand, replacing Gly with Ala increases helix stability by about 1 kcal/mol (over extended β-strand) in both α- and 3_{10}-helices.[4,5] Thus, the H-bonding energies suggest the β-sheet structure to be intrinsically more stable than the α-helix when the influence of the environment and the primary (the specific amino acid sequence) and tertiary structures are not taken into account. These observations are consistent with the suggested molecular bases for amyloid diseases as extended β-sheets could easily be more thermodynamically stable than helices under the proper conditions.

Conclusions

Hydrogen-bond cooperativity plays an important role in the energetics of the association of β-strands to form β-sheets. However, the cooperativity in the interstrand H-bonds is tempered by the effects of the association upon the energies of the intrastrand C_5 H···O interactions, which can be strengthened or weakened when the strands associate to form a sheet. These effects mask the inherent cooperativity of the H-bonding chains to the extent that the association of β-strands to form β-sheets can become anticooperative overall, as in the formation of 4GLY4S from four GLY4 strands, where 10 of the 12 C_5 interactions originally present in the four strands are weakened or destroyed in the sheet. Large H-bonding rings (such as that in 2GLY2L) are more stable than small ones (such as that in GLY2S) by about 9−10 kcal/mol. The quantity of each type of H-bonding ring correlates well with the relative energies of each pair of structures made from the GLY2 and GLY4 strands (those that resemble α-amino acids). The current studies are limited to planar structures of C_{2H} symmetry composed of strands of glycine and glycine-like residues. While these are the largest completely optimized structures for β-strands reported to date, they differ somewhat from the pleated structures common in many proteins. The cooperative interactions discussed in this paper clearly would be affected by structural variation; however, the basic qualitative conclusions should remain.

The H-bonds in β sheets are calculated to be more stable and shorter than those of α-helices calculated by the same method that were previously reported.

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Supporting Information Available: Cartesian coordinates of the relevant structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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