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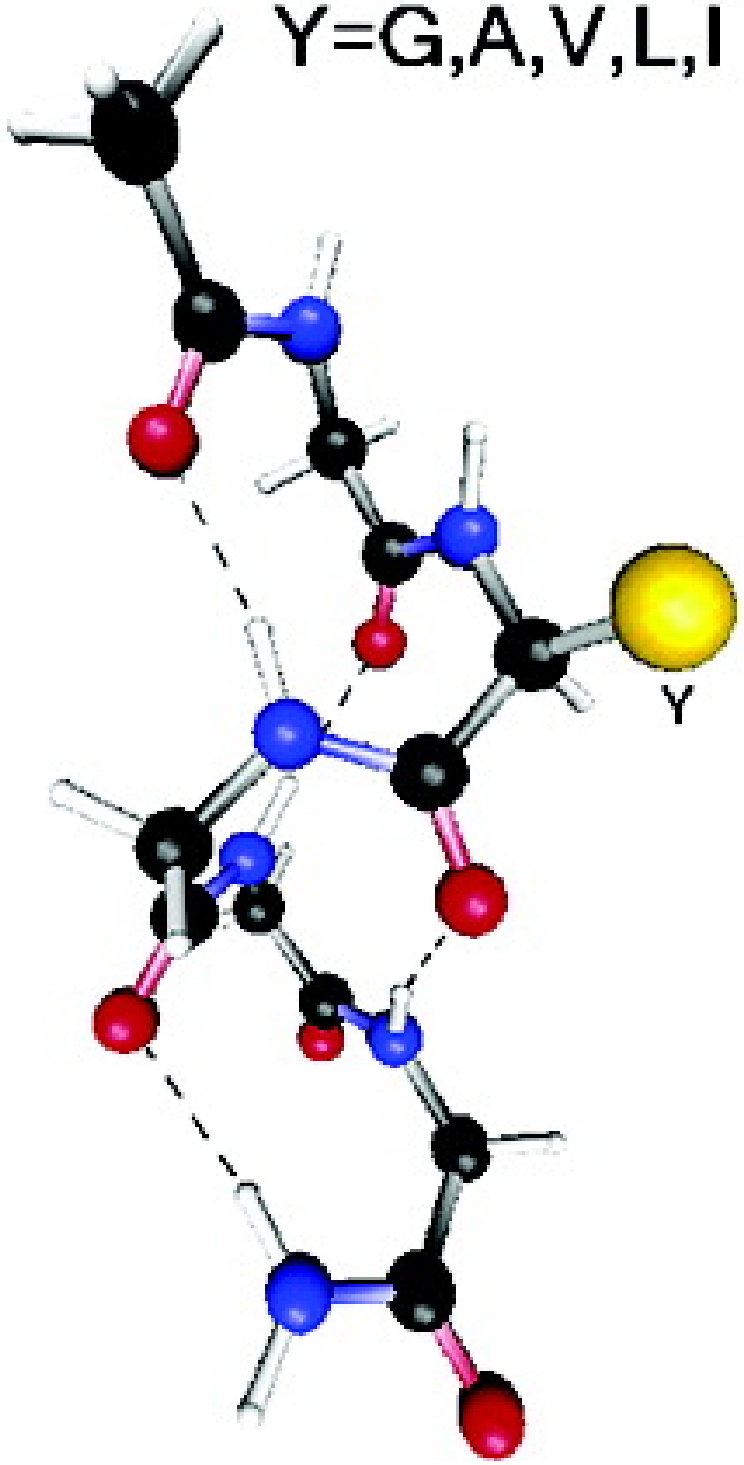
Acetyl-GYGGG-NH_2

Y=G,A,V,L,I



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Hydrogen-Bond Cooperativity, Vibrational Coupling, and Dependence of Helix Stability on Changes in Amino Acid Sequence in Small 3_{10}-Helical Peptides. A Density Functional Theory Study

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Abstract: Five pentapeptides, GGGGG, GAGGG, GVGGG, GLGGG, and GIGGG, have been completely optimized in the 3_{10}-helical and open β-strand conformations at the B3LYP/D95** level. The energies of the helices relative to the β-strands vary from -2.1 to -3.6 kcal and depend on the amino acid residue sequence. The energies of substituting A, V, L, or I for G in the second position are also presented. Vibrational analyses were performed on the optimized structures. Vibrational coupling through the individual H-bond chains of the helices is confirmed to be stronger than that through space or through the covalent bonds. The cooperative interactions of the H-bonds are evident from both the structures and the coupling of the amide I, amide II, and N−H vibrations.

The importance of cooperative H-bonding to the understanding of peptide structure is becoming increasingly apparent from both theoretical and experimental studies. We have previously reported that theoretical studies of hydrogen bonds in chains of formamide molecules show a very high degree of cooperativity.[1,2] The enthalpies of H-bonds in a chain of 15 formamides vary from 1.7 to 2.9 (average 2.6) times that of a dimer. We have also reported that the amide I, amide II, and N−H hydrogen bonding vibrations are also very strongly coupled for chains of formamides, much more so than for polyglycines containing equivalent numbers of amide residues.[3] Kemp has shown that an important enthalpic contribution to α-helix formation derives from cooperative H-bonding.[4] Other published examples of H-bond cooperativity within amides have been limited to small systems or those where the cooperativity involves solvent molecules.[5−7] The studies involving solvent molecules can be important if one compares the energies of helical peptides with extended conformations in H-bonding solvents such as water.

For this paper, we have used the B3LYP/D95** method to determine the energies and geometries of pentapeptides in their 3_{10}-helical and extended β-strand conformations. We shall not directly address the solvent effects on these relative energies in this study. To address the effects of solvation, one must first understand the intrinsic energetics of the isolated system. We have not been able to find stable α-helical minima for peptides this short, in agreement with other theoretical studies.[8] Thus, the peptides that we consider here are probably too short to form α-helices. The energetics of conversion and the relative stabilities of 3_{10} and α-helices have been extensively studied experimentally.[9−14]

We have chosen five pentapeptides for this study. They are polyglycine and a polyglycine in which the second amino acid is replaced by alanine, A, valine, V, leucine, L, and isoleucine, I, respectively. Each peptide is terminated with an acetyl group at one end and an NH_2 at the other (see Figures 1 and 2). We chose these peptides for several reasons. First, with up to 56 atoms and 162 internal degrees of freedom, they are sufficiently small so that complete optimization and vibrational calculations can be performed using reasonable DFT methods. Determination of the vibrational frequencies from the calculated potential energy surface requires a well-defined energy minimum as a starting point. Only complete geometric optimization can provide this. This allows us to observe the effects of changes in amino acids upon both the geometries and the vibrational spectra. Second, we selected a set of peptides which differ only

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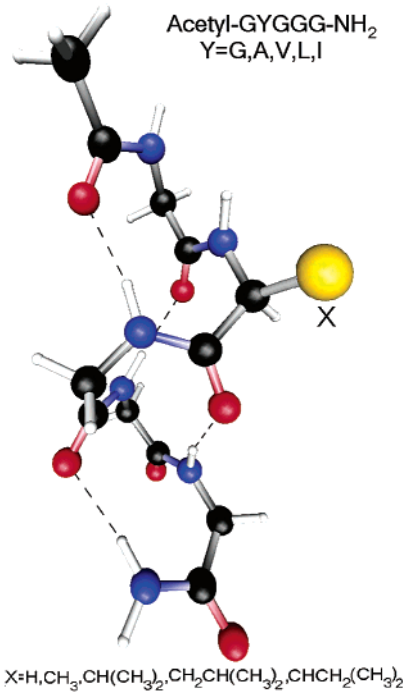

Figure 1. Structures of the helical peptides studied.

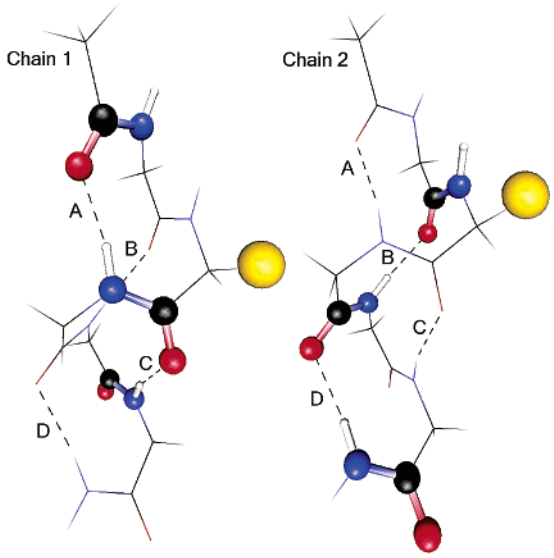

Figure 2. H-bonding chains in the helical peptide structures.

slightly so that we could determine the effects upon helix stability and vibrational frequencies of varying individual residues. Third, we limited the amino acids chosen to those without H-bonding donor or acceptor sites on the side chain to eliminate the possibility of interference by these sites upon the helical H-bonding system. In solution, such H-bonding sites on side chains would likely interact with solvent without greatly affecting the helical H-bonds. In our model calculations, they could interact with the amidic H-bonding sites to affect the relative stabilities of the helices.

Methods

We used the Gaussian 98 suite of computer programs[15] to perform hybrid DFT calculations at the B3LYP/D95(d,p) level. This method combines Becke's three-parameter functional,[16] with the nonlocal correlation provided by the correlation functional of Lee, Yang, and Parr.[17] We used our cluster of Intel and AMD powered computers that are parallelized using LINDA[18] for these calculations. The number of nodes used for each calculation varied with the sizes of the systems studied. The vibrational frequencies were calculated for the planar and helical structures, using the normal harmonic approximations employed in the GAUSSIAN 98 program to verify the stationary points, to calculate the enthalpies of the various species, and to discuss and compare the vibrational frequencies. All frequencies were real. The frequencies reported here have not been modified by any scaling factor.

The amide I frequencies were calculated for comparison with the DFT results using the nondegenerate extended coupled oscillator (NECO) method of Diem,[19] which treats the C═O's as coupled dipoles appropriately oriented in space.

Table 1. Energies and Enthalpies (298 K) of β-Strand to Helix Conversion and of Reaction 1 for Helices and Strands[a]

			GGGGG + Y → GYGGG + G			
GYGGG	β-strand → helix		helix		β-strand	
Y =	energy	enthalpy	energy	enthalpy	energy	enthalpy
G	−2.09	−0.78				
A	−3.00	−1.77	−1.03	−1.03	−0.13	−0.04
V	−2.76	−1.60	−1.22	−1.23	−0.55	−0.42
L	−3.60	−2.49	−2.41	−2.31	−0.89	−0.61
I	−2.77	−1.68	−1.29	−1.19	−0.61	−0.30

[a] Energies in kcal/mol.

Results and Discussion

The data in Table 1 show that, while the energy of helix formation from the β-strand for acetylGGGGGNH$_2$ is −2.1 kcal/mol, the corresponding values for the four other peptides are all almost 1 kcal/mol larger in magnitude. Thus, alkylation of the second glycine to form A, V, I, or L all favor helix formation even *in the absence of solvation*. This observation can be due to a relative destabilization of the open β-strand or relative stabilization of the 3_{10} helix upon alkylation or some combination of both. The geometric data of Table 2 clearly show that alkylation of the glycine causes a significant change in the optimized helical geometry of the pentapeptide. These data indicate that the H-bonds are shorter (on average) for the alkyl substituted helical structures than for acetylGYGGGNH$_2$. Since shorter H-bonds are generally stronger, this suggests that the substituted helices may be more stable.

$$\text{acetylGGGGGNH}_2 + \text{Y} \rightarrow \text{acetylGGGGGNH}_2 + \text{G} \quad (1)$$

In the optimized β-strand, acetylGGGGGNH$_2$ is essentially planar, but all four substituted peptides have a definite kink at the position of substitution (see Figure 3). Kinks of this type lead to the pleated sheet structures that are generally found in proteins.[20,21] Only glycine residues can form planar β-strands

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Table 2. Geometric Parameters for the H-Bonds in the Helical Peptides[a]

	distance or angle					difference from GGGGG			
peptide	GGGGG	GAGGG	GVGGG	GLGGG	GIGGG	GAGGG	GVGGG	GLGGG	GIGGG
				H-bond A					
R (O..N)	3.035	3.034	3.044	3.041	3.043	−0.001	0.009	0.006	0.008
R (O..H)	2.029	2.028	2.037	2.034	2.035	−0.001	0.008	0.005	0.006
O..H−N	169.6	169.5	169.5	169.8	169.8	−0.1	−0.1	0.2	0.2
CNCC	−65.5	−65.6	−65.8	−65.6	−65.7	−0.1	−0.3	−0.1	−0.2
NCCN	−24.0	−23.2	−22.6	−22.3	−22.4	0.8	1.4	1.7	1.6
				H-bond B					
R (O..N)	3.144	3.123	3.076	3.073	3.070	−0.021	−0.068	−0.071	−0.074
R (O..H)	2.141	2.119	2.074	2.071	2.067	−0.022	−0.067	−0.070	−0.074
O..H−N	168.7	168.8	168.2	168.2	168.1	0.1	−0.5	−0.5	−0.6
CNCC	−60.8	−59.8	−59.4	−56.6	−59.4	1.0	1.4	4.2	1.4
NCCN	−18.0	−20.4	−21.6	−26.2	−21.5	−2.4	−3.6	−8.2	−3.5
				H-bond C					
R (O..N)	3.162	3.172	3.162	3.141	3.149	0.010	0.000	−0.021	−0.013
R (O..H)	2.165	2.172	2.162	2.141	2.149	0.007	−0.003	−0.024	−0.016
O..H−N	166.7	167.5	167.5	167.9	167.5	0.8	0.8	1.2	0.8
CNCC	−62.8	−62.9	−62.1	−61.2	−61.9	−0.1	0.7	1.6	0.9
NCCN	−17.8	−17.1	−18.0	−17.7	−17.8	0.7	−0.2	0.1	−0.6
				H-bond D					
R (O..N)	3.167	3.147	3.142	3.134	3.139	−0.020	−0.025	−0.033	−0.028
R (O..H)	2.178	2.158	2.162	2.145	2.150	−0.020	−0.016	−0.033	−0.028
O..H−N	164.3	164.3	164.2	164.0	164.2	0.0	−0.1	−0.3	−0.1
	−68.0	−67.6	−67.7	−67.0	−67.5	0.4	0.3	1.0	0.5
	−9.6	−10.3	−10.1	−10.7	−10.1	−0.7	−0.5	−1.1	−0.5
				Average					
R (O..N)	3.127	3.119	3.106	3.097	3.100	−0.008	−0.021	−0.030	−0.027
R (O..H)	2.128	2.119	2.109	2.098	2.100	−0.009	−0.020	−0.030	−0.028
O..H−N	167.3	167.5	167.4	167.5	167.4	0.2	0.0	0.2	0.1

[a] Distances are in Å, and angles, in degrees.

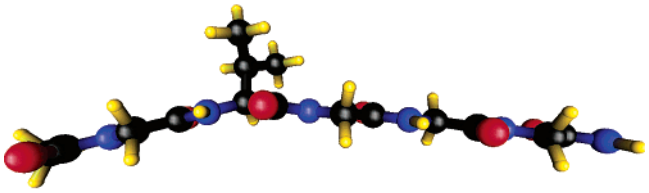

Figure 3. Extended β-strands illustrated for acetylGVGGGNH$_2$. Note the absence of H-bonds and the kink in the backbone at the position of the carbon atom substituted with the isopropyl group.

(and sheets). This observation suggests that the β-strands structure might be destabilized by the alkyl substituents.

To quantitatively determine the effects on the relative energies of the heterogeneous pentapeptides, acetylGYGGGNH$_2$, we determined the energies of the general reaction 1 for each of the amino acids (Y = A, I, L, V), for both the β-strand and 3_{10}-helical forms. The results (see Table 1) indicate that substitution of any of the amino acids, Y, for G stabilizes the helix significantly more than the β-strand. Thus, the apparent energetic effects based upon the shortening of the average H-bonds described above appear to be dominant. Of the amino acids considered, substitution by leucine most favors the helix over the beta sheet. Close examination of the individual helical structures shows that there can be small stabilizing interactions. The relative stability of the helical structures are clearly due to the stabilization of the H-bonds largely offsetting the strain induced upon helix formation. Other studies which have shown the large cooperative nature of amide H-bonds strongly suggest that larger helices should have significantly larger (than the 0.5−0.8 kcal/mol/H-bond) energetic stabilizations than those described here.[1,2] Conversely, smaller helices may not be stable relative to the β-strands. A recent report suggests the existence of a H-bond between the C−H bonds of the beta carbons of the side chains and an oxygen.[22] These are possible when Y = V, L, and I but not with Y = G or A. However, these interactions do not seem to explain (by themselves) the observed energy differences.

Examination of the enthalpic data at 298 K (Table 1) shows that the helical structures are less favored relative to the β-strands by approximately 1 kcal/mol when compared to the vibrationally uncorrected energetic data. One would expect those vibrational modes that involve relatively free rotation about the C−C bond in the β-strand to be significantly tightened in the helical structures, in qualitative accord with the difference between the energetic and the enthalpic data. Since these small helices owe their slight relative stabilities to the four H-bonds formed, the β-strands would probably be favored in an H-bonding solvent (such as water). H-bonds to the solvent could replace those of the helices with consequent relaxation of strain.

Geometries. The H-bonds are clearly affected by changing the amino acid at the second position, as indicated by the data in Table 2. The effects on the H-bonds in the second chain (H-bonds B and D) are somewhat larger than on the first (H-bonds A and C). Substitution of an H with an alkyl group may slightly affect the acidity of the N−H protons and the basicity of the C═O's and /or facilitate some weak C−H···O interactions between the alkyl group and the C═O in H-bond C. Other small conformational effects caused by the alkyl groups are also

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Table 3. Vibrational Frequencies and Relative Contributions to the Amplitudes of Each Amino Acid Residue (Amide I, Amide II, and N−H) for GGGGG and the Shifts from These Frequencies for the Other Peptides[a]

			Amide I			
			Frequency			
	1739.2 (1754.2)	1743.1 (1756.7)	1752.3 (1762.4)	1756.7 (1766.1)	1765.4 (1776.7)	1778.4 (1778.4)
			Amplitude			
C═O1	9 (2)	23 (21)	−40 (32)	27 (16)	2 (−28)	2 (1)
C═O2	−14 (−7)	0 (30)	27 (−1)	46 (−36)	7 (0)	1 (27)
C═O3	30 (22)	33 (−13)	26 (26)	−7 (−3)	10 (10)	0 (27)
C═O4	−37 (−31)	32 (4)	2 (17)	−15 (7)	1 (40)	11 (−1)
C═O5	4 (27)	5 (21)	6 (1)	5 (−11)	71 (10)	8 (31)
C═O6	5 (−11)	6 (−12)	0 (24)	0 (−28)	9 (−11)	79 (−14)
			Frequency Shift from GGGGG			
GAGGG	−2.5	−2.3	−3.1	−2.8	−0.3	−0.7
GIGGG	−3.0	−3.1	0.7	0.2	2.9	−0.7
GLGGG	−4.5	−4.0	−2.9	−2.8	−0.3	−1.0
GVGGG	−6.3	−4.1	−4.2	−3.3	−0.3	−1.1
			Amide II			
			Frequency			
	1523.7	1537.1	1547.6	1563.5	1564.8	1622.1
			Amplitude			
C−N1	78	−10	1	0	8	0
C−N2	9	44	−27	14	13	0
C−N3	13	19	8	−14	−50	4
C−N4	0	20	29	31	27	7
C−N5	0	−8	33	39	2	−20
C−N6	0	0	1	2	0	68
			Frequency Shift from GGGGG			
GAGGG	0.9	−1.4	−1.3	−2.3	−1.5	−3.3
GIGGG	0.6	−0.6	0.3	−5.3	−1.9	−5.4
GLGGG	0.5	0.0	0.6	−3.4	−0.7	−4.5
GVGGG	0.1	−1.4	0.2	−5.0	−0.6	−3.8
			N−H			
			Frequency			
	3543.2	3563.0	3573.6	3576.8	3648.0	3656.7
			Amplitude			
NH1	1	0	0	0	90	9
NH2	0	0	1	0	9	90
NH3	87	1	2	−8	1	0
NH4	2	21	77	5	0	1
NH5	9	−5	−3	84	0	0
NH6	1	74	−17	3	0	0
			Frequency Shift from GGGGG			
GAGGG	0.6	−4.1	−4.9	−0.6	1.4	−5.2
GIGGG	6.2	−4.5	3.9	3.9	−16.6	−9.2
GLGGG	0.6	−6.2	−11.2	−3.4	−1.4	−7.0
GVGGG	2.6	−6.6	−8.2	−2.3	−3.6	−6.6

[a] Frequencies are in cm^{-1}. The numbers in parentheses are calculated using the NECO dipole interaction model for the amide I vibrations (see text).

possible. However, these subtle effects are difficult to interpret unambiguously.

Vibrational Frequencies. The vibrational frequencies for the amide I, amide II, and N−H vibrations are presented in Table 3 and Figures 4−6. Table 3 also contains the results (in parentheses) of a model calculation for the amide I frequencies in which the C═O's are simply treated as isolated dipoles. We used the Cartesian coordinates of the carbons and oxygens in the six C═O's to position and orient the dipoles. Since this calculation provides relative frequencies, we arbitrarily aligned the highest frequency with that of our DFT calculation for purposes of comparison. To facilitate the discussion, the figures categorize the relative amplitudes of the contribution of each glycine residue with respect to the position of each H-bond in the two H-bonding chains.

A. Amide I. The DFT amide I (C═O stretch) vibrations are red shifted in the helices from their respective values in the β-strand by about 4 cm^{-1} based upon the average of the four H-bonding C═O's as compared to the lowest four vibrations of the β-strand or by 14 cm^{-1} if compared to the average of all six C═O stretches in the β-strand. The two vibrations of the C═O's (amide I vibrations 5 and 6) that are not H-bond acceptors only couple weakly with the other four. The relative amplitudes are taken from the C═O displacements. Only the four H-bonding C═O's are plotted in Figure 4. The coupling between the C═O's involved in the H-bonds show the expected order within each H-bond chain (the symmetric stretches are more red shifted). However, the *antisymmetric* coupling between the *symmetric* stretches of the two chains is the lowest frequency by about 4 cm^{-1}.

Comparison with the vibrations calculated using the NECO method demonstrates the differences in the couplings between the C═O's as treated by NECO and DFT (see Table 3). Since NECO calculated relative frequencies, we arbitrarily aligned the

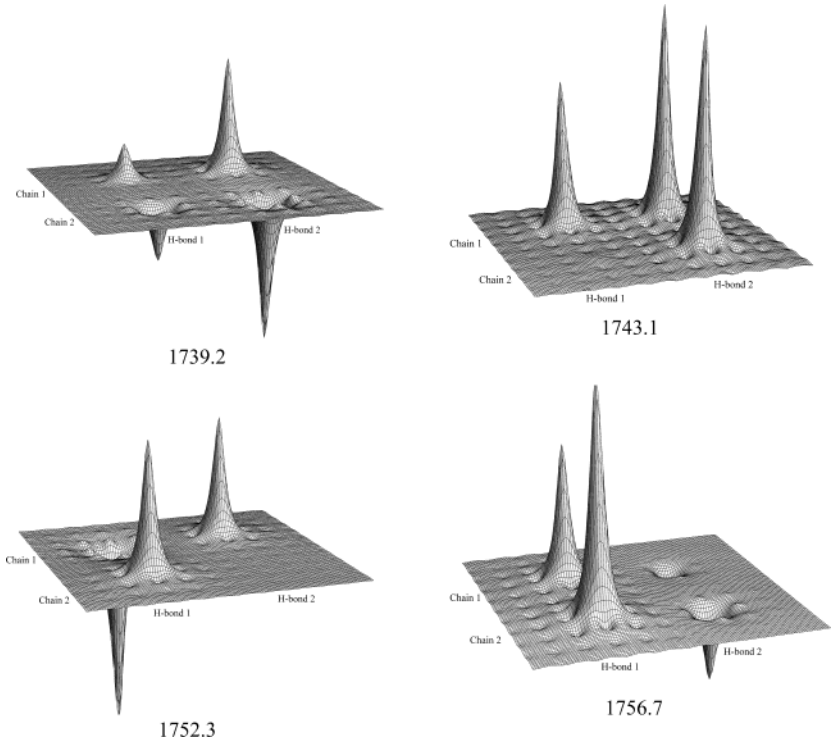

Figure 4. Amplitudes of each C═O stretch in the amide I coupled vibrations distinguished by the H-bonding chain for acetylGGGGGNH$_2$. The frequencies (cm^{-1}) are listed beneath each surface. The coupling for the lowest frequency can be seen to be in-phase *within* the chains but out-of-phase *between* them, while the reverse obtains for the highest frequency.

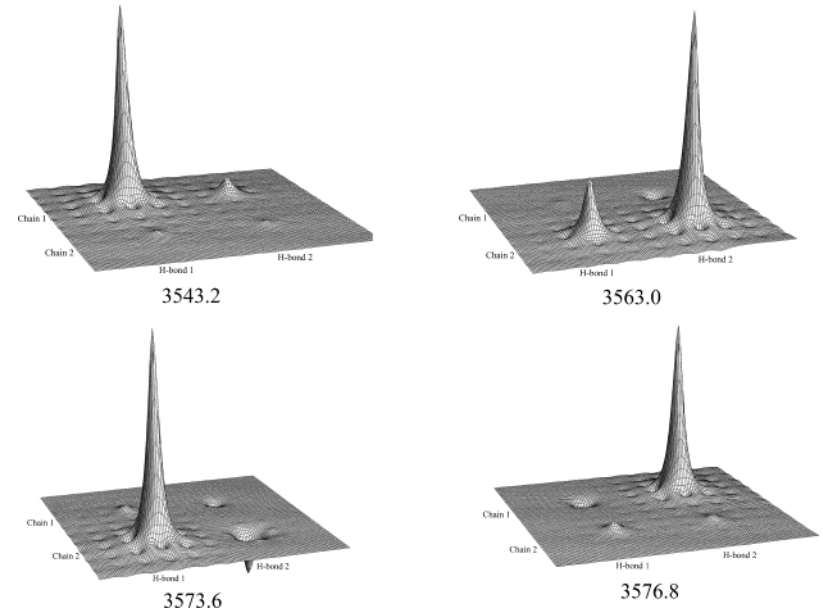

Figure 5. Amplitudes of each N−H stretch in the coupled N−H H-bonding vibrations distinguished by the H-bonding chain for acetylGGGGGNH$_2$. The frequencies (cm^{-1}) are listed beneath each surface

highest frequencies in the amide I region as calculated by each method. The range of frequencies for the DFT calculation (39.2 cm^{-1}) is over 50% greater than that predicted by NECO (24.2 cm^{-1}). The strongest absorption in the amide I region as predicted by DFT is the second most red shifted, coming at 1743.1 cm^{-1}. The corresponding vibration has all the C═O's except one stretching in concert while one does not move, thus providing the greatest change in dipole moment. In the NECO model, the strongest absorption is the third most red shifted, coming at 1762.4 cm^{-1}. In this vibrational mode, four of the six C═O's stretch in concert, while the other two remain essentially still. The differences between the two sets of calculated amide I frequencies can be attributed to the vibrational coupling that acts within the H-bonding chains. In the DFT calculation, the two C═O's (5 and 6 in Table 1) that do not participate in the H-bonds do not couple significantly with any of the other C═O's (not even with each other), while the vibrational frequencies calculated using NECO predict that they should couple extensively with the other four C═O's. Conversely, the C═O's within each H-bonding chain couple most strongly with each other in the DFT calculations. The larger red shifts associated with the vibrational modes that involve

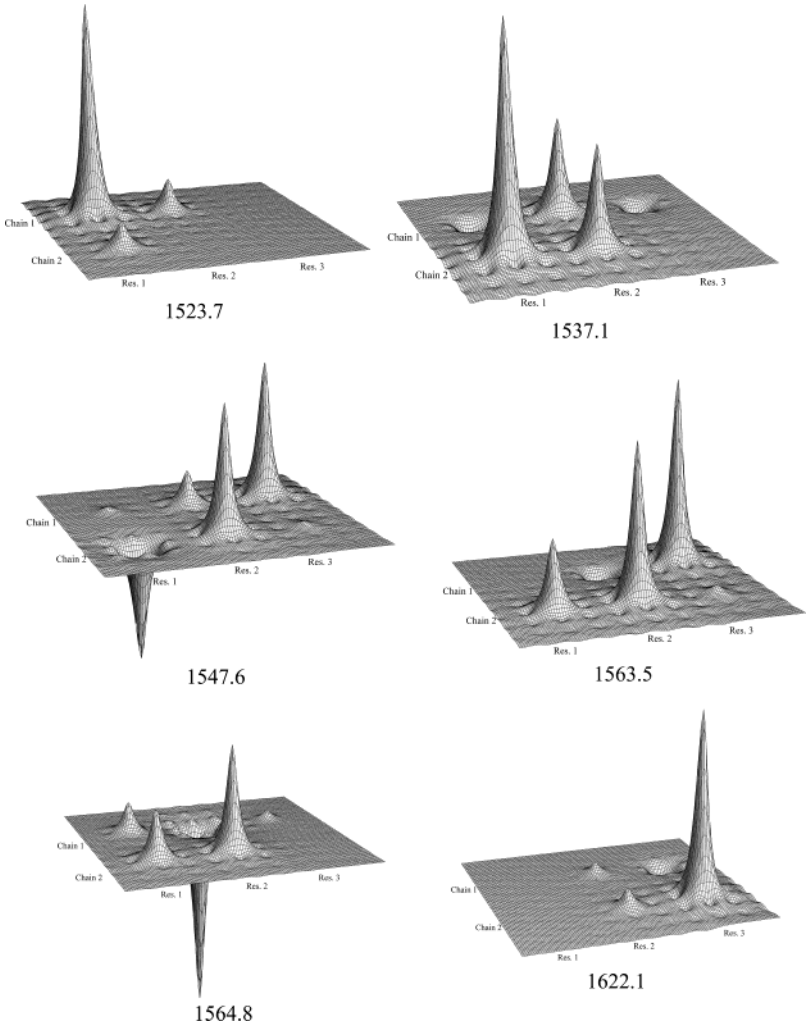

Figure 6. Amplitudes of each C−N stretch in the amide II coupled vibrations distinguished by the H-bonding chain for acetylGGGGGNH$_2$. The frequencies (cm^{-1}) are listed beneath each surface.

the C═O's coupled through the H-bonds in the DFT calculated vibrations as compared with those calculated using NECO (where there are no explicit H-bonds) highlight the relative importance of the coupling within the H-bonding chains. The enhanced coupling of the C═O's through the H-bonding chains confirms the cooperativity of the H-bonds within each chain. While qualitatively consistent with a dipole−dipole interaction of the two *dimeric H-bond chains*, the DFT result is inconsistent with the NECO dipole model involving all six C═O's. However, it is consistent with our observation that amide I coupling is strongest through the H-bonds in a comparison of H-bonded formamides and β-strand polyglycine.[3]

B. N−H Stretching. The N−H (H-bonding) stretches for the GGGGG helix are depicted in Figure 4. The first two amides, which do not provide H-bonding donors, are not included in the figure. The most red-shifted vibration involves primarily the first H-bond in the first chain (A in Figure 2) weakly coupled with the second H-bond in that chain (C). The next vibration (about 20 cm^{-1} higher) primarily involves the second H-bonding chain with most of the intensity in H-bond D. The splitting between the primarily symmetric and antisymmetric combinations of the H-bonds in chain 2 (10.6 cm^{-1}) is significantly less than that for the H-bonds in chain 1 (33.6), presumably because the terminal amide of chain 2 is different from the others due to the NH$_2$. The N−H stretches for the four H-bonding N−H's in the helix are red shifted by 18 cm^{-1} when compared to the average of the five N−H's of the β-strand (the NH$_2$ was excluded from the average).

C. Amide II. The amide II vibrations for the GGGGG helix are the most complicated. The relative contributions of the individual glycine residues are taken as the C−N displacements (which are assumed to be representative of the more complex vibration). These are depicted in Figure 5. Here, we show the contributions of all six vibrations as they are all involved in at least one H-bond as either a donor or an acceptor. The terminal NH$_2$ is clearly different from the other amides which are all N-substituted. The first two amides are only H-bond acceptors and the next two are both donors and acceptors, while the last two (including the NH$_2$) are only donors. As a result, the couplings show a rather complex pattern. The lowest frequencies have large contributions from the first two amides (acceptors), while the highest frequencies have their largest contributions from the last two amides (donors). The center of the amide II band is blue shifted from the β-strand by about 3 cm^{-1} if one does not consider the NH$_2$ vibration. Calculated frequencies for some similar systems have been reported recently by Keiderling et al.[8,23] They also used DFT calculations with a slightly smaller basis set (6-31G*) and some imposed constraints. We generally

(23) Kubelka, J.; Gangani, R. A.; Silva, D.; Keiderling, T. A. *J. Am. Chem. Soc.* **2002**, *124*, 5325.

prefer the D95 over the 6-31 series of basis sets for H-bonding systems as the former generally have smaller basis set superposition errors (BSSE).[24] Since the methodology for calculating BSSE-corrected geometries and frequencies for interactions *between* molecules[25] has not been perfected for interactions *within* molecules (such as peptide H-bonds), we favor the basis sets that have the smaller errors. Their reported frequencies[8,23] are qualitatively similar, although generally a bit smaller than those reported here. They did not discuss the coupling between the components of the individual peptide linkages in detail. Krimm has reported vibrational calculations on larger peptides, particularly α-helical polyalanine, using force fields derived from ab initio calculations.[26,27]

Conclusions

DFT calculations indicate that GGGGG and GYGGG show small preferences for 3_{10}-helix formation from β-strands. This preference would likely increase with the size of the peptides as the cooperativity of the H-bonds in the chains would make them relatively stronger as the chains grow. This preference is somewhat diminished when the enthalpies are considered rather than the total energies. Substitution of Y for G to form GYGGG stabilizes the helix more than the β-strand relative to GGGGG for all cases studied.

The coupling of the C═O stretches (amide I vibrations) is greater within the H-bonding chains (Figure 2) than through the covalent bonds or by dipole−dipole coupling in accord with earlier work that compared H-bonding chains of formamides with extended β-strands of polyglycine.[3] The dipoles of the H-bonding dimers in each chain (rather than the individual C═O's) appear to couple by the dipole−dipole mechanism to make the *antisymmetric* combination the lowest frequency amide I vibration. The coupling of the amide II and N−H stretches are more complex as discussed in the text.

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Supporting Information Available: Cartesian coordinance of the five optimized peptides. This material is available free of charge via the Internet at http://pubs.acs.org.

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