Communication

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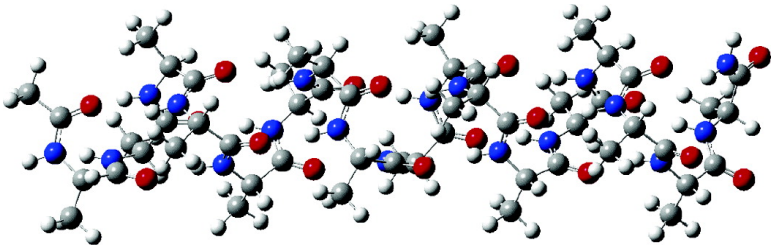

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Enthalpies of Hydrogen-Bonds in α-Helical Peptides. An ONIOM DFT/AM1 Study

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The energetics of α-helix formation remains an important subject for peptide chemistry. Several recent reports, both experimental[1−3] and theoretical,[4−13] indicate α-helical formation to be enthalpy dominated, at least for polyalanines, in contrast to earlier suggestions that folding be entropy controlled.[14,15] The (unfolded) nonhelical state, often referred to as the random-coil, has recently been shown to primarily assume the polyproline II conformation in aqueous solution for polyalanine peptides too short to form α-helices.[16−18] Other studies also confirm the nonrandom nature of unfolded proteins.[19,20]

Experimental enthalpies of helix formation from the nonhelical state have been reported for various α-helices. These measurements have been difficult to compare with theoretical values for two major reasons: (1) the theoretical results have been reported as energies, ΔE, in contrast to the measured enthalpies, ΔH; and (2) the energies of the helices need to be compared to a suitable reference that corresponds to the unfolded state.

In this communication, we provide the theoretical values for the incremental ΔH's for formation of α-helices (Figure 1) from extended β-strands (Figure 2) for capped polyalanines, acetyl-$(Ala)_nNH_2$, with $n = 8$, 10, 12−17. We have previously reported the optimized geometries and energies of these species.[4] Starting from these optimized geometries, we used the GAUSSIAN 03[21] program to calculate the vibrational frequencies of all of these α-helices using the same methods reported previously:[4] ONIOM,[22] where the entire peptide backbone was calculated at the high level (B3LYP/D95**) and only the methyl groups at the low level (AM1[23]). The enthalpies are obtained from the vibrational analysis. Similar vibrational analyses were obtained for the optimized extended β-strands previously reported for up to $n = 10$. The $\Delta\Delta H$'s (differential ΔH) for each type of structure upon addition of another alanine (i.e., the difference in the ΔH for acetyl$(Ala)_nNH_2$ − that for acetyl$(Ala)_{(n-1)}NH_2$ for two consecutive values of n) were calculated. As in our previous reports, we relate the enthalpies and energies to the component amino acids using the imaginary polycondensation reaction: n Ala + CH_3COOH + NH_3 → acetyl-$(Ala)_nNH_2$ + n H_2O. The differential ΔH for the extended β-strands reach their asymptotic limit of −1.4 kcal/mol for $n = 10$, so no larger β-strands were subjected to vibrational analysis. The differential ΔH's for the α-helices are both more negative and continue to increase in magnitude as n increases due to the H-bond formation and the accompanying cooperative interactions. They have not quite reached their asymptotic limits for $n = 17$.

Ab initio calculations of H-bonding interactions are subject to basis set superposition error (BSSE). The counterpoise (CP) correction[24,25] has generally been used to correct for BSSE. However, this correction usually is applied to two or more molecular species that form an aggregate, rather than to two different conformations of the same species, only one of which contains H-bonds. Nevertheless, the same kinds of BSSE should occur in the latter case as the placement of the basis functions changes relative to the H-bond donors and acceptors upon going from one conformation to another, despite the fact that the number and types of basis functions remain the same. This error leads to artifactually stronger and shorter H-bonds. The CP correction can be used to correct for BSSE either a posteri (with a single-point CP calculation using a previously optimized geometry)[24,25] or the structures can be optimized on a CP-corrected surface.[26] The problem of the definition of the interacting fragments for a polypeptide makes calculating the BSSE difficult for either method. In a previous report, we found the CP correction to be reasonably constant at about 1.2 kcal/mol/H-bond for chains of H-bonding formamides.[27] For this study, we estimated the CP correction for the H-bonds in each helix by extracting a formamide dimer for each H-bond from the optimized helix and capping the C−C and C−N bonds with H's. For the first H-bond (which is bifurcated), we use one formamide and the terminal fragment containing the two donor protons. Since the a posteri CP method was used, the CP corrections should be taken as upper limits to the true BSSE. Consequently, the calculated CP-corrected differential H-bond ΔH's are lower limits (in magnitude).

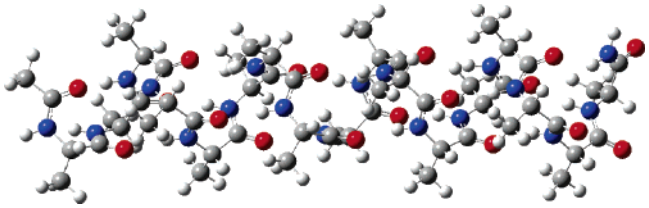

Figure 1. α-Helical acetyl$(Ala)_{17}NH_2$.

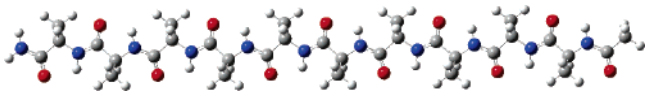

Figure 2. Extended β-strand of acetyl$(Ala)_{10}NH_2$.

The data are presented in Table 1. We could not obtain the differential ΔH's for $n = 8$, 10, and 12, as we could not find stable α-helical structures for $n < 8$, 9, or 11. We present the data for the planar and helical structures (Table 1) in several different ways. In addition to the ΔH's, themselves, we present the values per alanine (n), per H-bond ($n - 2$, as the acetyl contributes a C═O, donor), and as incremental ΔH's ($\Delta\Delta H$'s), defined as the change in the difference in enthalpy (helix-strand) upon addition of one Ala to the peptide.

The ΔH's include the zero-point vibration correction and the proper Boltzmann distribution over the vibrational levels at 298 K. While one might suppose that the more rigid helix would have a significantly higher (incremental) vibrational correction upon

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Table 1. Helix-Strand Differential Enthalpies, ΔH, as a Function of n in Acetyl(Ala)$_n$NH$_2$. H Represents the Incremental Change in H (the value for n less that for $n - 1$)

n	ΔH	ΔH/H-bond	$\Delta\Delta H$	ΔH/Ala
8	3.15	0.53		0.39
9				
10	0.62	0.08		0.06
11				
12	−0.10	−0.01		−0.01
13	−2.13	−0.19	−2.03	−0.16
14	−4.11	−0.34	−1.98	−0.29
15	−6.44	−0.50	−2.33	−0.43
16	−9.20	−0.66	−2.76	−0.57
17	−11.99	−0.80	−2.79	−0.71

addition of an alanine, the values for the helix and strand are virtually the same and constant at 56.4 and 56.2 kcal/mol, respectively.

After correction for BSSE, the smallest α-helix with a negative $\Delta\Delta H$ (helix-strand) is for $n = 12$. The largest helix considered ($n = 17$) has a ΔH 0f −11.99 kcal/mol (which translates to −0.80 per H-bond or −0.71 per Ala). However, the incremental helix-strand $\Delta\Delta H$'s, while still increasing in magnitude at $n = 17$, probably will reach the asymptotic limit around −3 kcal/mol (in contrast to approximately −7 kcal/mol for the ΔE).[4] Thus, one can expect the enthalpic stability per H-bond of the helix over the strand to continue to increase with n until the peptide grows much larger.

The value of ΔH/H-bond of −0.8 kcal/mol for $n = 17$ is remarkably close to that measured by Baldwin (0.9 kcal/mol per Ala) for polyalanines of similar size (note that there are two more Ala's than H-bonds in our structures);[2] however, he reports no variation with the size of the peptide. One might expect the experimental enthalpy difference between α-helical and unfolded polyalanines to favor the helices less than the gas phase values as the unfolded state is more conformationally mobile, thus, better adapted to assuming a structure that can be optimally solvated. Both experimental[16,17] and theoretical[18] reports indicate that short polyalanines assume the polyproline II structure in aqueous solution (rather than the β-strand favored in the gas phase) agrees with this hypothesis.

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Supporting Information Available: The complete citation for GAUSSIAN 03 (ref 21). This material is available free of charge via the Internet at http://pubs.acs.org.

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