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Density Functional Theory Study of β-Hairpins in Antiparallel β-Sheets, a New Classification Based upon H-Bond Topology

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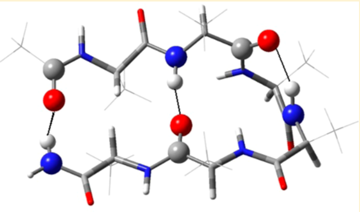

ABSTRACT: We present a new classification of β-turns specific to antiparallel β-sheets based upon the topology of H-bond formation. This classification results from ONIOM calculations using B3LYP/D95** density functional theory and AM1 semiempirical calculations as the high and low levels, respectively. We chose acetyl(Ala)$_6$NH$_2$ as a model system as it is the simplest all-alanine system that can form all the H-bonds required for a β-turn in a sheet. Of the 10 different conformations we have found, the most stable structures have C$_7$ cyclic H-bonds in place of the C$_{10}$ interactions specified in the classic definition. Also, the chiralities specified for residues *i* + 1 and *i* + 2 in the classic definition disappear when the structures are optimized using our techniques, as the energetic differences among the four diastereomers of each structure are not substantial for 8 of the 10 conformations.

We have recently extended our theoretical studies of β-sheets to include the effects of β-turns on their relative stabilities.[1] In the course of these studies, we noted that most of the β-turns that formed in the 36 geometrically optimized structures of acetyl(Ala)$_N$NH$_2$ (N = 28 or 40) studied contained C$_7$ cyclic H-bonds in place of the C$_{10}$ H-bonds expected from the standard β-turn structures. These observations led us to undertake the more detailed study of β-turns presented here.

We have previously shown that density functional theory (DFT) calculations predict isomeric dimeric structures of a diglycine analogue (see Figure 1) to have very different H-bonding energies, with the large ring structure (ΔH = −14 kcal/mol) favored by ∼9 kcal/mol over the small ring (ΔH = −5 kcal/mol).[2] Perczel has reported similar results.[3] Larger models of β-sheets have energies (corrected for differences in cooperativity) that differ by the same amount depending on whether they contain one more large than small ring or the reverse.[2] Other isomeric cyclic H-bonding structures exhibit similar characteristics.[4] From the foregoing, we expect the C$_{10}$ H-bond would have a ΔH of approximately −2.5 (half of the stabilization of the small ring by its two H-bonds) if in an isolated system. Certainly, the C$_{10}$ H-bond should be substantially weaker than the C$_{14}$ H-bond, which is part of a large ring. Thus, we expect that many β-turns may have a C$_{10}$ interaction in which the H-bond might be broken or severely weakened. Furthermore, breaking the C$_{10}$ H-bond may facilitate the formation of one of several possible C$_7$ H-bonding interactions involving the donor or acceptor of the broken C$_{10}$ H-bond.

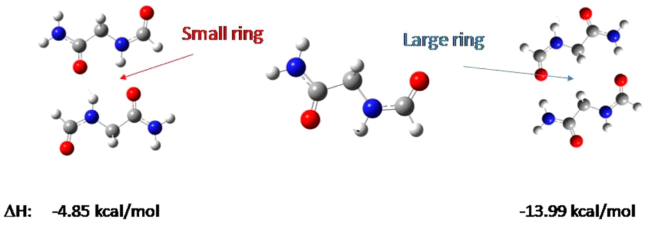

Figure 1. Calculated ΔH_{int} values for two isomeric cyclic H-bonding dimers of formylGlyNH$_2$ (center). The $\Delta\Delta H_{int}$ between the dimers (∼9 kcal/mol) is maintained for larger models of glycine β-sheets that contain one more large than small ring (see ref 2).

The original definition of type β-turns described by Venkatachalam[5] and reviewed by Rose[6] assumes the C$_{10}$ H-bond between the residues *i* and *i* + 3 to be intact. These turns are divided into different types based upon the ϕ and ψ dihedral angles of residues *i* + 1 and *i* + 2 within the turn. While this definition might be relatively straightforward in small model systems, it is not at all easy to ascertain from X-ray crystallographic evidence obtained from the protein database, as the positions of the H atoms cannot be determined. The N···O distance constitutes the best measure of the existence (or not) of the C$_{10}$ interaction that can be obtained from these crystal structures. However, if the C$_{10}$ H-bond breaks in favor of a C$_7$ while the C$_{14}$ remains intact, the N···O distance may not increase by very much because of the remaining constraints including the C$_{14}$ ring and the rigidity of the peptide links ($\omega \sim 180°$). Certainly, the N···O distance cannot increase by an amount nearly as large as the H···O distance. In principle, the ring defined by the C$_{10}$ H-bond can break in either a conrotatory or disrotatory (terminology borrowed from the orbital symmetry rules[7]) fashion. In the former, the C═O and N−H bond vectors both turn in the same sense (clockwise or counterclockwise) and in the latter in opposite senses. In the former, the O···H distance will increase very quickly with the amount of rotation and in the latter somewhat less. In both

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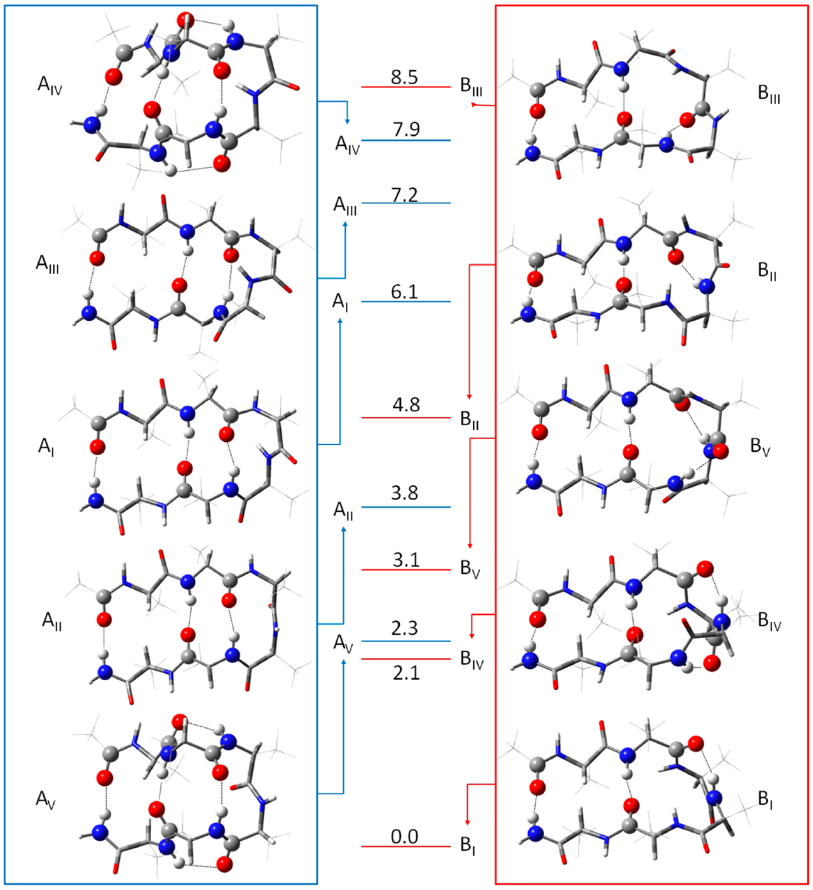

Figure 2. Type A and B turns with relative energies (kilocalories per mole) for the all-L-Ala structures.

cases, the O···H distance should increase much more than the N···O distance. Some X-ray crystal structures put the N···O distance for the putative C_{10} H-bond at 3.2–3.5 Å, and nuclear magnetic resonance (NMR) studies suggest that this H-bond may be weaker than interactions with solvent.[6]

There have been many other criteria used to define β-turns that rely on crystallographic data.[6] One of the earliest, that the Cα–Cα distance between residues i and $i + 3$ be less than 7 Å and the structure not be helical,[8] is still widely used.[9] This definition (as it does not depend upon dihedral angles) does not distinguish between types I and II, or between types A and B as defined below. It does eliminate type III (which is helical). We have optimized geometries of β-turns that fit this definition. In our hands, this distance in all optimized β-turns is <5.7 Å. We shall use the <5.7 Å limit in this paper.

The original definitions of type II and II′ β-turns also require that residues $i + 1$ and $i + 2$ be of opposite chiralities.[5] This would require all natural proteins that have only L residues to form only type II or II′ β-turns if at least one of the residues is Gly. The origin of this requirement appears to come from the original modeling of Venkatachalam.[5]

To model those β-turns that exist in β-sheets, one needs to consider peptides that contain at least six amino acids if capped by an acetyl at the N-terminus and that are not cyclic, as previously noted. For a peptide, this is the smallest size that can allow the C_{10} H-bond to open while keeping the C_{14} as part of the large ring interaction between strands. In the absence of the adjacent full large ring, the C_{10} interaction will be stronger than when it is present for the reasons discussed above. However, larger structures that contain several strands in the β-sheet provide much better models, as the turn structure can be affected by H-bonding from proximate strands on either side.

In this paper, we present DFT calculations using the ONIOM two-layer protocol on different conformations of β-turns formed from acetyl(Ala)$_6$NH$_2$, the smallest polyalanine model of a β-turn that is sufficiently large to include the C_{14} cyclic H-bond structure that is expected to weaken the adjacent C_{10} H-bond.

■ CALCULATIONAL DETAILS

We used the ONIOM[10,11] method as programmed in the GAUSSIAN 09[12] suite. ONIOM divides the system into up to three segments that can be treated at different levels of calculational complexity. Thus, one can treat the essential part of the system at the high level, while the less critical parts of the system might be calculated at the medium or low level. For this study, we used only two levels (high and low). We treated the backbones of each of the individual peptides at the high level, with only the side chains (methyls of the alanines and acetyl cap) at the low level. The high level used hybrid DFT methods at the B3LYP/D95(d,p) level. This method combines Becke's three-parameter functional[13] with the nonlocal correlation provided by the correlation functional of Lee, Yang, and Parr.[14] In the ONIOM method, there are unsatisfied valences in the high level at the interface between it and the low level. These valences were satisfied by using the default method of capping them with a hydrogen atom in the direction of the connecting atom in the low level with a C–H distance that was 0.723886 times the C–C distance. We used the AM1[15] semiempirical molecular orbital method for the ONIOM low level.

With the ONIOM method, GAUSSIAN performs a high-level (DFT) calculation only on those atoms designated with the valences terminated as described above.

All geometries were completely optimized in all internal degrees of freedom. Vibrational calculations confirmed that the reported geometries are true minima on the PESs as there are no imaginary vibrational frequencies. We used these frequencies to calculate the enthalpies of optimized species.

In a previous study of five 17-amino acid peptides,[16] we found little difference in the relative energies between this procedure and another where the side chains (in this case, the methyls) were subsequently optimized using DFT, with the (previously optimized) peptide chain held fixed. The current procedure also gave relative energies that agreed well with complete DFT optimizations for a series of five small 3_{10}-helical peptides.[17] We recently found this procedure to give reasonable results when compared to several pure DFT (including several that are parametrized to include dispersion, which we found to be generally unreliable for peptides) methods for peptides and results from experimental databases.[18] B3LYP/D95** also gives reasonable results for H-bonding interactions.[19,20]

■ RESULTS

Figure 2 presents the structures of all the optimized conformations of acetyl(L-Ala)$_6$NH$_2$ that we have found and indicates the enthalpies of each relative to the most stable structure, B$_I$. We have divided them into two classes: (A) those that contain a C$_{10}$ cyclic H-bond and (B) those that do not. Table 1 compares the calculated relative enthalpies for these and similar structures that have one or two D-Ala residues at positions i + 1 and/or i + 2. Table 2 presents the MUE's (mean unsigned errors) for the i + 1 and i + 2 ϕ and ψ dihedrals from the standard values indicated for type I, I′, II, and II′ β-turns. All attempts to find DL or DD structures of type B$_{III}$ converged to the more stable B$_I$ structures. We also could not find another possible structure containing a C$_7$ H-bond involving the i + 2 C=O group. Several attempts converged to the A$_I$ structure.

Table 1. Relative Enthalpies (kilocalories per mole) for Isomers of Acetyl(Ala)$_6$NH$_2$ Designated by the Chirality of Residues i + 1 and i + 2

turn	LL	DD	DL	LD
A$_I$	6.1	1.4	4.6	2.9
A$_{II}$	3.8	3.5	3.0	4.4
A$_{III}$	7.2	9.8	9.5	7.5
A$_{IV}$	7.9	2.8	7.6	3.1
A$_V$	2.3	1.6	1.6	2.2
B$_I$	0.0	0.0	0.0	0.0
B$_{II}$	4.8	2.1	6.7	0.2
B$_{III}$	8.5			7.7
B$_{IV}$	2.1	1.6	2.7	0.9
B$_V$	3.1	2.6	5.4	0.3

The MUE's of Table 2 show that the A$_I$ structure correlates best with the turn normally defined as type I′, A$_{II}$ correlates best with that normally defined as type II′, and A$_{III}$ correlates best with type I. The A$_{IV}$ and A$_V$ structures have dihedrals that best correlate with types I′ and II′ but contain additional C$_7$ H-bonds. These correlations hold for all four diastereomers of the turns despite the definition holding that only the LL diastereomer should form type I, only DD should form type I′, and only DL should form type II′. We note that the LD diastereomer does not form the expected type II. In fact, we located no structures that correspond to type II despite multiple attempts form different starting geometries, including some resulting from partial optimizations with constraints designed to find likely type II structures. We also note that very few of the correlations mentioned have MUE's of <10 and that

Table 2. Mean Unsigned Errors (MUE's) with Respect to the Standard ϕ and ψ Dihedrals for Type I, I′, II, and II′ β-Turns As Defined by Rose for Isomers of Acetyl(Ala)$_6$NH$_2$ Designated by the Chirality of Residues i + 1 and i + 2

	I	I′	II	II′
		A$_I$		
LL	94	6	61	84
DD	97	17	72	87
DL	97	14	69	87
LD	93	9	64	83
		A$_{II}$		
LL	60	90	140	11
DD	57	87	137	7
DL	61	91	141	11
LD	57	88	137	8
		A$_{III}$		
LL	19	97	87	74
DD	8	93	83	63
DL	15	97	87	70
LD	15	94	84	67
		A$_{IV}$		
LL	106	18	73	96
DD	102	16	71	92
DL	104	17	72	94
LD	102	15	70	92
		A$_V$		
LL	55	82	132	5
DD	64	84	134	9
DL	58	84	134	4
LD	61	82	132	7
		B$_I$		
LL	43	73	123	25
DD	52	76	126	23
DL	47	77	127	26
LD	48	72	122	23
		B$_{II}$		
LL	77	48	21	127
DD	81	51	32	131
DL	73	43	22	123
LD	85	55	32	135
		B$_{III}$		
LL	51	138	128	62
LD	50	133	123	59
		B$_{IV}$		
LL	64	89	139	35
DD	68	88	138	36
DL	68	92	142	36
LD	64	85	135	35
		B$_V$		
LL	89	67	28	139
DD	94	67	31	144
DL	85	62	28	135
LD	89	62	30	139

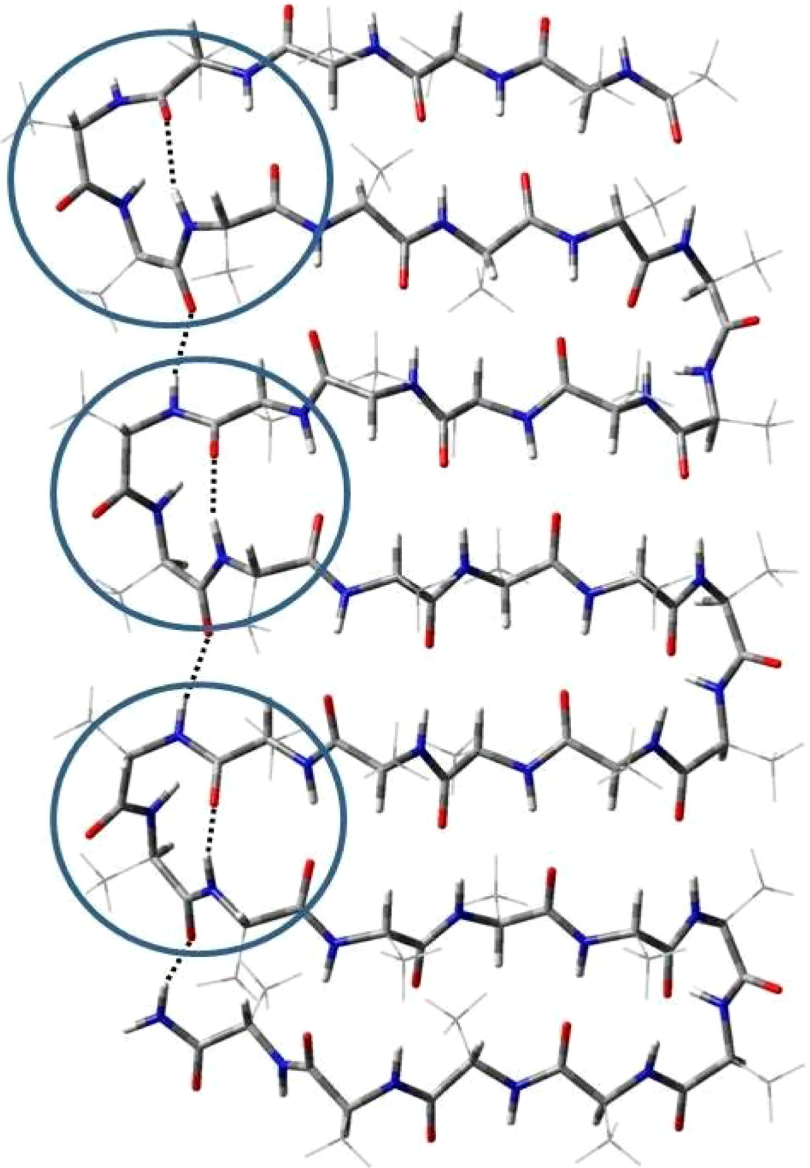

Figure 3. Structure of optimized acetyl(Ala)$_{40}$NH$_2$ with six β-turns taken from the Supporting Information of ref 1. Circles identify three A$_{III}$ turns that have dihedrals that correspond to type I turns. Dashed lines indicate a H-bonding chain that likely stabilized these turns.

several of those correspond to matches with types that should not occur with the chirality of the residues involved (i.e., LL A$_I$ for type I′, DD A$_{III}$ for type I, and LL A$_V$ for type II′). Five of the 10 structures found do not correspond to any of those defined by Venkatachalam[5] and Rose.[6] The overall most stable structure for each of the diastereomers, B$_I$, contains a C$_7$ rather than a C$_{10}$ H-bond. Even in the structures that contain C$_{10}$ H-bonds, these H-bonds are considerably distorted by pucker above or below the quasi-plane of the turn, as seen in Figure 2.

■ DISCUSSION

In the context of these results, we suggest a different classification for β-turns occurring in β-sheets. We begin by defining a β-turn as having at least one H-bond between residues *i* and *i* + 3. In fact, two such H-bonds are possible: (a) one between the N−H (donor) group of residue *i* and the C═O (acceptor) group of residue *i* + 3 and (b) the other between the C═O group of residue *i* and the N−H group of residue *i* + 3. The former creates a H-bonding cyclic system containing 14 atoms (including the H) defined as C$_{14}$. The latter defines a C$_{10}$ ring. We note that the C$_{10}$ ring we discuss is not helical. Thus, it differs from that of the 3$_{10}$-helix or the turn sometimes described as type III or III′. We have previously reported a structure similar to this for a smaller trialanine model structure (32L).[21] We also note that turns in β-sheets differ from those in many of the small systems in which β-turns have been studied. In β-sheets, the turns are framed by multi-H-bond interactions between the adjacent strands that comprise that part of the sheet whose direction is reversed by the turn. The foregoing may not be true in many small structures that have been studied in detail. We believe this difference to be important as the H-bond that defines the C$_{10}$ H-bonding ring will be particularly weak as its breakage removes one small ring from the sheet structure but leaves the large adjacent large ring intact.

We define the two classes of β-turns in terms of whether the turn contains both C$_{14}$ and C$_{10}$ H-bonds (class A) or just the

C_{14} H-bond (class B). Thornton has proposed a somewhat related but different classification.[22]

Three of the five kinds of class A turns (see Figure 2) that we have found through geometry optimization differ in how the C_{10} H-bond is puckered (up or down) with respect to the quasi-plane of the structure and with the orientation of the amide coupling between residues $i + 1$ and $i + 2$. The A_{IV} and A_V turns contain additional C_7 H-bonds between residues i and $i + 1$ and between residues $i + 2$ and $i + 3$, which are not likely to be found in real β-sheets. The A_I turn has dihedrals that resemble those of a type I′ turn, which should only occur with the DD diastereomer. While this conformation exists for all four diastereomers, the DD diastereomer is the most favorable of them, only 1.4 kcal/mol less stable than the global minimum B_I turn. The A_{III} structure most resembles the type I turn (although the MUE's are substantial), especially for the LL diastereomer, which is the one required by the traditional definition of type I. However, the LL diastereomer (while significantly above the global minimum) is the most stable of the A_{III} structures. The A_{II} structure most resembles the classic type II′ turn. It, too, can be found for all four diastereomers. The DL isomer has the lowest energy compared to the global minima for this structure. However, it is the lowest-energy class A structure (discounting A_{IV} and A_V) that should be possible in a β-sheet for the LL diastereomer as well as the DL diastereomer.

We identified five optimized class B turns (see Figure 2). All of these lack the C_{10} H-bond and contain one or two C_7 H-bonds in its stead. We shall characterize these interactions by listing the two residues involved (H-bond donor to acceptor). Both the B_I structure, the global minimum, and B_{II} structures contain an H-bond from residue $i + 1$ to i. They differ in the direction of the pucker of this interaction with respect to the quasi-plane of the structure. The B_{III} structure has an H-bond from residue $i + 3$ to $i + 2$. The B_{IV} and B_V structures both have two C_7 H-bonds from residue $i + 3$ to $i + 2$ and from residue $i + 2$ to i. They differ in the orientations of the H-bond puckers about the quasi-plane of the structure. For the LL diastereomer, B_I, B_{IV}, and B_V are all more stable than any A structure except for A_V. For the LD diastereomer, all B structures except B_{III} are more stable than all A structures.

We emphasize that isolated turns all contain unsatisfied H-bond donors and acceptors, which should become satisfied under experimental conditions. Etter has promulgated a set of rules that pertain to H-bonds in organic crystals.[23] Her first rule is "all good proton donors and acceptors are used in hydrogen bonding." Hairpins that contain the H-bonding donors present in the amide group (C═O and N−H) must be stabilized by H-bonds in crystal structures according to Etter's first rule. The structure of a derivative of VV-D-PGVV, which has two molecules and two bridging water molecules between the exposed amides in the unit cell that interact via H-bonds, reported by Isabella Karle[24] clearly follows this rule. In a recent paper, Rose has challenged the assumption that proteins form additional H-bonds when they fold.[25] Combining Etter's rule with Rose's findings, one might reasonably assume that all of the C═O and N−H groups in crystalline proteins must have their H-bonds satisfied by water (ordered or disordered) or something else in the crystal. Our DFT results suggest that the strongest H-bonds will be formed in the absence of solvent, leaving the weaker one unsatisfied. Thus, the stronger C_7 H-bond forms at the expense of the weaker C_{10} H-bond. Similar behavior may often be found in solution or in crystals when one considers the H-bonding interactions with the environment. While the C_{10} H-bond is weak in the turn as it resides in a small ring, there is no reason for the components of the broken C_{10} H-bond to interact more weakly via H-bonds with the environment. We are currently investigating the effects of aqueous solvation on these structures using combinations of explicit interactions with water molecules and solvent continuum models as we have done for α-helices.[26] As solvation should have a strong influence on entropic effects, we intend to include the evaluation of these effects in this forthcoming study.

In a recent theoretical study of the energetics of polyalanine β-sheets as a function of the number of β-turns using the same methods used here, we found B_{II} turns to be the most common. Among examples of type A β-turns that we have encountered in this study, we found dihedral angles close to those suggested for A_{III} (similar to type I) for several structures classified as "D" (the least stable of the four kinds of β-sheet structures we found), especially that with 40 residues and six turns despite the present observation that such (A_{III}) structures are ∼7 kcal/mol less stable than B_I.[1] These turns in these structures are buttressed by H-bonds to proximate strands of the sheet (see Figure 3), and the "D" structures are the least stable of the four types that we identified. We note that the full crystal lattice (as opposed to the unit cell) of the type II′ structure found by Karle (see above) also is buttressed by H-bonds formed from sheets involving other unit cells.[24] However, the results of our calculations and those of other groups differ substantially from the suggested dihedrals for type II β-turns. Often, substantial differences from the suggested dihedrals (±30) are tolerated for the assignment of type II β-turns. Some prefer to simply define type II turns in terms of regions of the Ramachandran surface rather than use specific values of the dihedrals.[27]

In our studies of β-turns in polyalanine β-sheets, we have encountered $C\alpha-C\alpha$ distances of 4.9−5.7 Å,[1] which confirm that these can be appropriately classified as β-turns. Many of these turns do not conform to any of the earlier definitions (type I, type II, etc.) that classify them as functions of ϕ and ψ about residues $i + 1$ and $i + 2$. Table 3 compiles the maximum

Table 3. Maximum and Minimum Values for the Parameters Taken from 108 β-Turns from 36 Optimized Structures of Acetyl(Ala)$_{28}$NH$_2$ and Acetyl(Ala)$_{40}$NH$_2$[a]

	maximum	minimum
$C\alpha\cdots C\alpha$	5.66	4.94
	C_{14} H-Bond	
O···N	3.04	2.76
O···H	2.03	1.79
	C_{10} H-Bond	
O···N	4.44	2.75
O···H	3.63	1.74
	C_7 H-Bond	
O···N	3.24	2.80
O···H	3.27	1.96
	Dihedrals	
	$i + 1$	
ϕ	78	−87
ψ	120	−117
	$i + 2$	
ϕ	171	−123
ψ	31	−104

[a] Distances in angstroms and angles in degrees.

and minimum values for the distance parameters of the H-bonds together with those for the ϕ and ψ dihedrals for residues $i + 1$ and $i + 2$. We obtained these data from 108 turns in 36 structures that were completely optimized using the same methods employed here. The values for the C_{14} H-bond distances (N···O and H···O) clearly indicate this H-bond to be intact in all structures. On the other hand, the same parameters for the C_{10} H-bond indicate this bond is intact only some of the time, as do those values that pertain to the putative C_7 H-bond. The values for the torsional angles, ϕ and ψ, vary considerably from those defined for type I, I′, II, and II′ β-turns in the earlier literature. The ranges of values for ϕ (78° to −87°) and ψ (120° to −117°) for residue $i + 1$ agree best with the standard values (60° to −60° and 120° to −120°), while that for ϕ of residue $i + 2$ (from 171° to −123° vs 90° to −90°) shows the greatest discrepancy. Nevertheless, all of these turns can be described as β-turns because of the Cα−Cα distances (table 1), as already noted.

While theory or empirical modeling can clearly define the presence or absence of a C_{10} H-bond needed for our proposed classification, experimental verification may not be so simple. Two experimental methods are generally used to gather information about the existence of a C_{10} H-bond: crystal structures and NMR. Because one cannot usually deduce the position of H-bonds from X-ray diffraction of crystals, and neutron diffraction studies have not been applied to proteins, one must use another criterion. The most obvious choice might be the N···O distance. While several studies of the N···O distances for the C_{10} H-bond have appeared, we know of none that specifically examined the possible C_7 N···O distances, nor do we know of NMR data that have been used to examine the extent of C_7 H-bond formation in β-turns.

■ CONCLUSIONS

Our proposed classification of β-turns within sheets primarily rests upon the existence (or not) of a C_{10} H-bond between residues i and $i + 3$ in the turn. Earlier work has shown the H-bonds in the small rings of β-sheets are significantly less stable than those of large rings. In β-turns, the C_{10} H-bond participates only in a small ring. In many cases, the formation of a C_7 H-bond in place of a C_{10} H-bond provides increased stabilization. The most stable conformation found, B_I, contains such a C_7 H-bond. The traditional classification of these turns into types I, I′, II, and II′, based upon hard-sphere modeling, requires specific chiralities for the residues $i + 1$ and $i + 2$. We find that these requirements might indicate small energetic preferences in some cases but that they do not hold in general. We believe that this new classification should help clarify the structural requirements for β-turns.

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Notes

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