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Helix Formation in α,γ- and β,γ-Hybrid Peptides: Theoretical Insights into Mimicry of α- and β-Peptides

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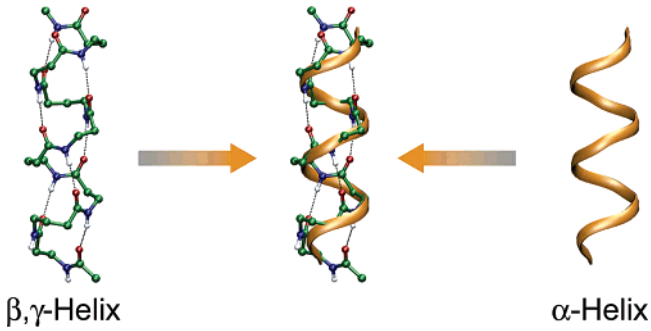

α,γ- and β,γ-hybrid peptides, which are composed of two different homologous amino acid constituents in alternate order, are suggested as novel classes of peptide foldamers. On the basis of a systematic conformational search employing the methods of ab initio MO theory, the possibilities for the formation of periodic secondary structures in these systems are described. The conformational analysis provides a great number of helix conformers widely differing in energy, which can be arranged into three groups: (i) helices with all hydrogen bonds formed in forward direction along the sequence, (ii) helices with all hydrogen bonds in backward direction, and (iii) helices with alternate hydrogen-bond directions (mixed or β-helices). Most stable are representatives of β-helices, but their stability decreases considerably in more polar environments in comparison to helix conformers from the other two classes. There is a great similarity between the overall topology of the most stable hybrid peptide helices and typical helices of peptides which are exclusively composed of a single type of homologous amino acids. Thus, the helices of the β,γ-hybrid peptides mimic perfectly those of the native α-peptides as, for instance, the well-known α-helix, whereas the most stable helix conformers of α,γ-hybrid peptides correspond well to the overall structure of β-peptide helices. The two suggested novel hybrid peptide classes expand considerably the pool of peptide foldamers and may be promising tools in peptide design and in material sciences.

Introduction

The wide variety of characteristic secondary structure elements, which have been found in oligomers of homologous β-, γ-, and δ-amino acids over the past decade, make these peptide foldamers attractive from several points of view.[1] Obviously, these structures are able to mimic typical secondary structures of native α-peptides and proteins such as helices, β-strands, and reverse turns. Therefore, homologous amino acids might be useful tools in peptide and protein structure design to improve and to optimize peptide and protein properties. This strategy is supported by the fact that peptides modified in this way or peptides which are even exclusively composed of homologous amino acids are resistant against proteases and show biological activity.[2] Moreover, peptide foldamers might also be interesting for material sciences due to structural similarities to synthetic

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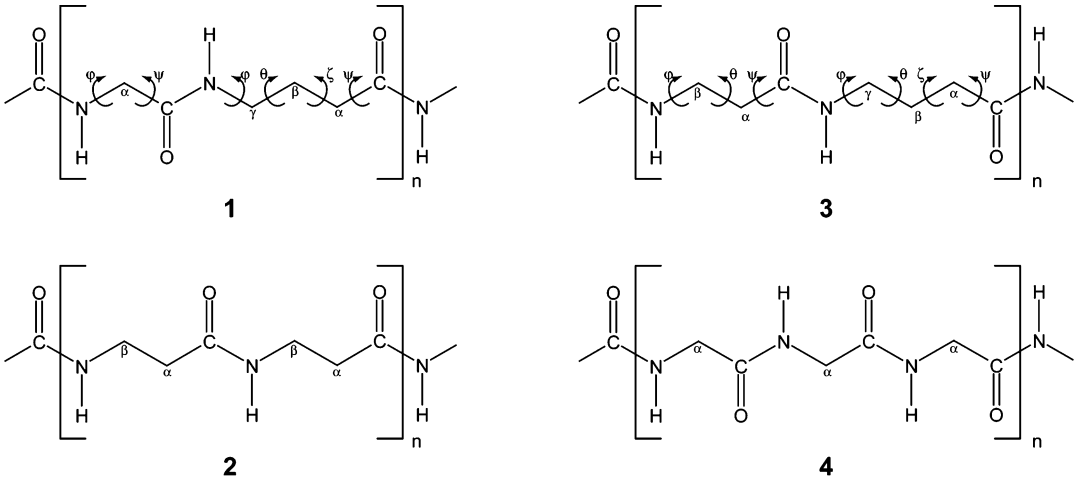

FIGURE 1. Schematic comparison between the dimeric units of α,γ-hybrid peptides (**1**) and β-peptides (**2**) and between a dimeric unit of a β,γ-hybrid peptide (**3**) and an α-tripeptide unit (**4**).

fibers and as novel scaffolds for nanotechnology.[1c,d,h,3i] Parallel to the considerable synthetic efforts in the field of peptide foldamers, which were accompanied by comprehensive structural analyses, secondary structure formation in these compounds was also examined employing the methods of ab initio MO theory. On the basis of theoretical calculations, it was possible to obtain a complete overview on the characteristic secondary structure elements in several classes of peptide foldamers as, for instance, in β-, γ-, δ-, aminoxy, and hydrazino peptides.[3] The most stable structures determined by the theoretical calculations are in excellent agreement with the typical secondary structures found in experimental structure analyses. In some cases, novel and unusual folding patterns were predicted,[3g−k] which could be confirmed by experimental studies afterward.[4]

Recently, the pool of peptide foldamers was expanded by hybrid peptides consisting of α- and β-amino acid monomers. Thus, the insertion of two consecutive β-amino acid constituents into an α-helix could be accomplished without significant structure distortion.[5a] Of particular interest are α,β-hybrid peptides composed of alternately changing α- and β-amino acid constituents.[5b−d] NMR studies provide convincing hints for the formation of special helix types in this novel foldamer class, but detailed geometry data are still missing. Here, we turn our attention to two further promising classes of hybrid peptides. One is composed of α- and γ-amino acid constituents, and the other consists of β- and γ-amino acid constituents in alternate order. Apart from the general interest in the possibilities of secondary structure formation in these novel hybrid peptides, another important structural aspect emerges. Contrary to alternating α,β-hybrid peptides, special secondary structure elements in the alternating α,γ- and β,γ-hybrid peptides should exhibit close relationships to typical secondary structure elements of α- and β-peptides as a comparison of the backbones shows (Figure 1).[6]

Referring to the aforementioned reliability of ab initio MO theory to correctly describe the preferred conformers in numerous foldamer classes, we give a complete overview on the formation of periodic secondary structures and their stabilities in the novel α,γ- and β,γ-hybrid peptides on the basis of a comprehensive conformational search. The focus is in particular on the similarities between secondary structure elements in the two hybrid peptide classes and those in sequences of α- and β-peptides illustrated in Figure 1. The suggestions of this study expand the field of foldamers and may stimulate the synthesis of peptide sequences with γ-amino acids, which is still in its initial phase.[7]

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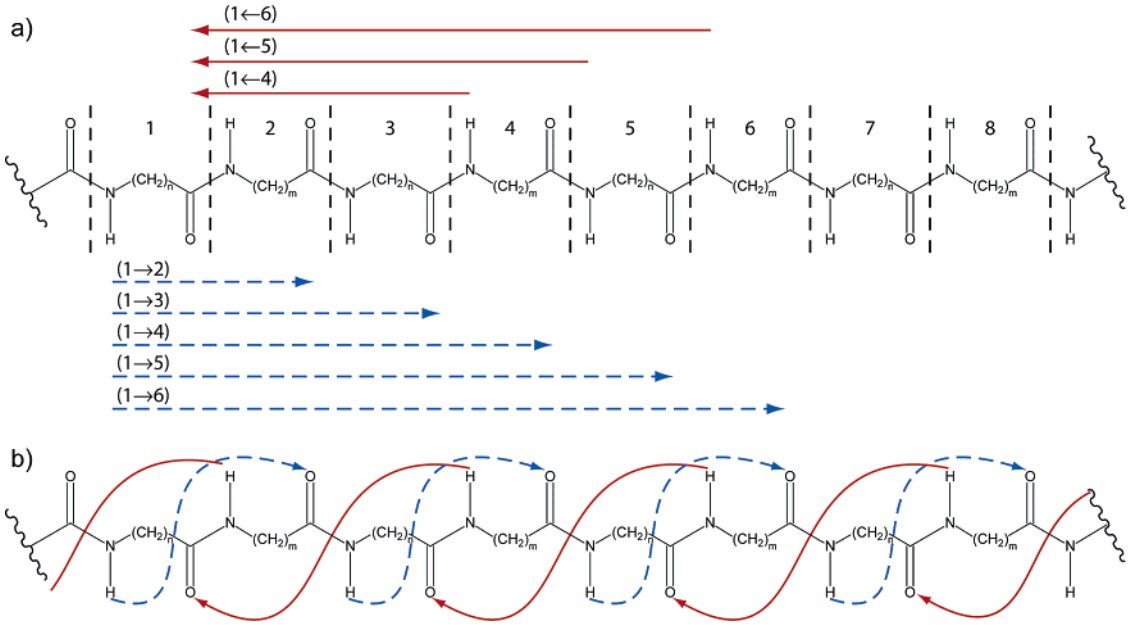

FIGURE 2. Possible hydrogen-bonding patterns for helices of hybrid peptides: (a) with exclusively forward or backward directions of the hydrogen bonds; (b) with hydrogen bonds alternately changing their directions (n/m = 1:α-amino acid, n/m = 2:β-amino acid, n/m = 3:γ-amino acid).

Methodology

A look at the sequences of α,γ- and β,γ-hybrid peptides shows three formal possibilities for periodic secondary structures with hydrogen-bonding interactions between non-nearest neighbor peptide bonds (Figure 2): (i) helices with all hydrogen bonds oriented in a backward direction along the sequence (Figure 2a), (ii) helices with all hydrogen bonds oriented in a forward direction of the sequence (Figure 2a), and (iii) helices with the hydrogen-bond directions alternately changing in backward and forward directions which are sometimes named "mixed" or β-helices (Figure 2b).[3j,8]

Due to the alternation of two different homologous amino acids, the periodicity of helices in hybrid peptides appears a priori at the level of dipeptide units. Contrary to this, the helices of homooligomers show the periodicity already at the monomer level provided that all hydrogen bonds are formed in the same direction. In this case, the corresponding backbone torsion angles of each amino acid constituent have the same values.

For each of the three basic helix types of the hybrid peptides, two alternative helical hydrogen-bonding patterns are possible. Table 1 provides an overview on all formal possibilities of helices with hydrogen bonding between non-nearest neighbor peptide bonds in only forward, only backward, and alternating forward and backward directions along the sequence up to interactions between amino acids in the positions i and $i \pm 5$. In the simplest helices with only backward hydrogen-bond orientations (see Figure 2a), the hydrogen bonds are formed either by 1 ← 4 amino acid interactions between the two different homologous amino acids (α/γ and γ/α or β/γ and γ/β) or by 1 ← 5 amino acid interactions between the same homologous amino acid constituents (α/α and γ/γ or β/β and γ/γ). In the first case, the alternating pseudocycles have the same size, but are structurally different; in the second case, the hydrogen-bonded rings resulting from the interactions between the same amino acid types are of different size (Table 1).

TABLE 1. Formal Possibilities of Hydrogen-Bonded Helices in α/γ- and β/γ-Hybrid Peptides

relative positions of interacting amino acids[a]	type of interacting amino acids[a,b]	hybrid peptide	alternating pseudocycles C_x/C_y[c]	helix notation
1←4	α←γ/γ←α	α,γ	C_{12}/C_{12}	H_{12}
	β←γ/γ←β	β,γ	C_{13}/C_{13}	H_{13}
1←5	α←α/γ←γ	α,γ	C_{17}/C_{15}	$H_{17/15}$
	β←β/γ←γ	β,γ	C_{18}/C_{17}	$H_{18/17}$
1←6	α←γ/γ←α	α,γ	C_{20}/C_{20}	H_{20}
	β←γ/γ←β	β,γ	C_{22}/C_{22}	H_{22}
1→2	α→γ/γ→α	α,γ	C_{10}/C_{10}	H_{10}
	β→γ/γ→β	β,γ	C_{11}/C_{11}	H_{11}
1→3	α→α/γ→γ	α,γ	C_{13}/C_{15}	$H_{13/15}$
	β→β/γ→γ	β,γ	C_{15}/C_{16}	$H_{15/16}$
1→4	α→γ/γ→α	α,γ	C_{18}/C_{18}	H_{18}
	β→γ/γ→β	β,γ	C_{20}/C_{20}	H_{20}
1→5	α→α/γ→γ	α,γ	C_{21}/C_{23}	$H_{21/23}$
	β→β/γ→γ	β,γ	C_{24}/C_{25}	$H_{24/25}$
1→6	α→γ/γ→α	α,γ	C_{26}/C_{26}	H_{26}
	β→γ/γ→β	β,γ	C_{29}/C_{29}	H_{29}
1→2/1←4	α→γ/α←γ	α,γ	C_{10}/C_{12}	$H_{10/12}$
	γ→α/γ←α	α,γ	C_{12}/C_{10}	$H_{12/10}$
	β→γ/β←γ	β,γ	C_{11}/C_{13}	$H_{11/13}$
	γ→β/γ←β	β,γ	C_{13}/C_{11}	$H_{13/11}$
1→4/1←6	α→γ/α←γ	α,γ	C_{18}/C_{20}	$H_{18/20}$
	γ→α/γ←α	α,γ	C_{20}/C_{18}	$H_{20/18}$
	β→γ/β←γ	β,γ	C_{20}/C_{22}	$H_{20/22}$
	γ→β/γ←β	β,γ	C_{22}/C_{20}	$H_{22/20}$

[a] →: forward direction. ←: backward direction of the hydrogen bonds. [b] α: α-amino acid. β: β-amino acid. γ: γ-amino acid. [c] x,y: number of atoms in the alternating hydrogen-bonded pseudocycles.

A comparable situation exists for the two hydrogen-bonding patterns of helices with a forward orientation of all hydrogen bonds (see Figure 2a). Now, the first helix type is realized by 1 → 2 amino acid interactions between different homologous amino acid types (α/γ and γ/α or β/γ and γ/β). Although structurally different, the alternating pseudocycles have again the same size. The alternative hydrogen bonding pattern is characterized by 1 → 3 amino acid interactions between the same homologous amino acid types (α/α and γ/γ or β/β and γ/γ) leading to alternating rings of different size (Table 1).

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The mixed or β-helices show some peculiarities. Here, the periodicity appears a priori at the dipeptide level even in sequences consisting exclusively of the same homologous amino acid constituents. Corresponding to this, the alternating hydrogen-bonded rings always have a different size and the hydrogen-bond directions alternate. The characteristic hydrogen-bonding patterns of the two mixed helix alternatives in hybrid peptides represent a combination of the above-mentioned amino acid interactions between the different homologous amino acids in backward and forward directions along the sequence (Figure 2b). The backward orientations result from 1 ← 4 amino acid interactions (α/γ or γ/α and β/γ or γ/β) and the forward orientations from 1 → 2 interactions (α/γ or γ/α and β/γ or γ/β)). It is important to note that the combination of α/γ (β/γ) interactions in backward direction with γ/α (γ/β) interactions in forward direction generates a mixed helix different from that obtained from the combination of γ/α (γ/β) interactions in backward direction with α/γ (β/γ) interactions in forward direction, even if the size of the corresponding alternating hydrogen-bonded rings is the same in the two β-helices (Figure 2b, Table 1). The detailed description given here concerns helices with the smallest possible sizes of hydrogen-bonded rings formed by non-nearest neighbor peptide bond interactions. Increasing systematically the sequence distances between the interacting amino acids leads to hydrogen-bonding patterns with still larger pseudocycles.

Our conformational search for all periodic secondary structures in α,γ- and β,γ-hybrid peptides followed strategies already employed for other peptide foldamers.[3g−j] Although it is known that a rigidification of the backbone by substituents or cyclization may favor secondary structure formation, we performed our studies on blocked peptide octamers with unsubstituted backbones. A special substitution pattern would enforce the folding into one or only few special secondary structure elements. Thus, the information on all principal folding patterns of the peptide backbones, which we want to obtain, gets lost. There are some further advantages of our strategy. The greater number of folding alternatives, which we can expect from our general conformational search, opens up the possibility for a synthetic chemist to think about special substitution patterns to favor the one or the other helix type. Finally, the pool of all helix conformers represents a good support for experimental structure analyses of these peptides. Thus, NMR data may immediately related to the various theoretically predicted conformers.

In the case of the α,γ-hybrid peptides, a pool of 1741824 conformations was generated by a systematic variation of the backbone torsion angles (φ,ψ) of the α- and ($\varphi,\theta,\zeta,\psi$) of the γ-amino acid constituents in blocked octamers in intervals of 30° considering the dipeptide periodicity (Figure 1). On the basis of general geometry criteria for hydrogen bonds, all conformations fulfilling the described hydrogen-bonding patterns were selected (Table 1, Figure 2). This procedure provided 88 conformations, which were starting points for complete geometry optimizations at the HF/6-31G* level of ab initio MO theory. The 6-31G* basis set has proved to be of sufficient reliability for the description of peptide structures.[9] In the larger alternating β,γ-hybrid peptide octamers, the backbone torsion angles φ and ψ of both homologous amino acid constituents were also varied in steps of 30°, but the torsion angles θ and ζ in 60° intervals. From the resulting 2612736 conformations, 94 starting conformations were selected for geometry optimization. Correlation effects on the structure were estimated by reoptimization of the HF/6-31G* conformers at the B3LYP/6-31G* level of density functional theory (DFT). For an estimation of the influence of an aqueous environment (dielectric constant $\epsilon = 78.4$), single-point calculations on the HF/6-31G* conformers were performed employing a polarizable continuum model (integral equation formalism for isotropic solvents: IEFPCM//HF/6-31G*).[10] Cavitation,[11a] dispersion, and repulsion energies[11b] are included in the solvation energies. All quantum chemical calculations were performed employing the Gaussian03 and Gamess-US program packages.[12]

Results and Discussion

Basic Helix Types in α,γ- and β,γ-Hybrid Peptides. Our systematic conformational search in both hybrid peptide classes provided numerous representatives for helices with exclusively forward or backward directions of the hydrogen bonds and mixed helices. In the α,γ-hybrid peptides, 47 out of the 88 starting conformations and in the β,γ-hybrid peptides 54 out of the 94 starting conformations kept the periodic hydrogen bonding patterns after geometry optimization. Comparing with the formally possible hydrogen-bonding patterns of Table 1, all helix types were confirmed with exception of $H_{13/15}$ in the α,γ-hybrid peptide series. Frequently, the same hydrogen-bonding pattern (Figure 2) can be realized by different backbone conformations. Thus, six conformers for the mixed helix type $H_{18/20}$ and seven conformers for the mixed helix types $H_{20/18}$ were found in α,γ-peptides. For the helix types $H_{20/22}$ and $H_{22/20}$ in the β,γ-hybrid peptides there exist even 10 and 9 conformational alternatives, respectively. The various folding alternatives for the same hydrogen-bonding pattern are denoted by superscript Roman figures at the helix symbol in the order of decreasing stability (see the Supporting Information). The HF/6-31G* backbone torsion angles of the most stable representative of each helix type in Table 1 are listed in Tables 2 and 3. The corresponding B3LYP/6-31G* data are given as Supporting Information. The structures of all 101 helix octamers are stored in pdb files (see the Supporting Information). As already confirmed by numerous studies on other foldamer classes, only the most stable backbone-folding patterns have a chance to be realized. From a dynamic point of view, most of the 101 helix

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TABLE 2. Backbone Torsion Angles[a] of the Most Stable Helices of Alternating α,γ-Hybrid Peptide Octamers at the HF/6-31G* Level of ab Initio MO Theory

helix[b]	φ	θ	ζ	ψ	helix[b]	φ	θ	ζ	ψ
H_{10}^{I}	−127.6			25.0	H_{20}^{I}	99.9			−22.1
	66.9	25.8	44.7	47.3		69.6	64.7	−153.4	−124.8
	92.9			137.9		79.1			17.2
	107.9	−53.4	75.8	61.2		78.4	55.4	174.4	−152.5
	100.3			137.9		87.6			−77.2
	105.7	−53.6	78.8	64.2		−142.1	66.6	178.8	176.2
	80.5			177.2		89.2			−62.8
	98.0	48.0	48.8	102.7		−155.3	66.8	175.1	162.4
H_{18}^{I}	96.5			146.3	$H_{10/12}^{I}$	141.9			−38.2
	71.4	175.2	174.1	108.3		−88.9	75.2	−75.6	160.1
	85.3			−72.8		128.3			−42.8
	−84.3	−177.8	177.1	107.3		−88.8	76.5	−76.1	159.5
	73.3			45.9		127.7			−42.3
	−132.9	−145.8	67.3	78.6		−88.8	76.6	−76.1	159.6
	93.6			−170.2		129.0			−44.8
	82.0	−176.5	70.5	103.9		−87.9	73.2	−78.0	159.6
$H_{21/23}^{I}$	−123.7			29.5	$H_{12/10}^{I}$	71.5			−147.8
	74.1	−179.5	−77.3	149.9		−64.8	−33.0	−47.8	130.2
	86.5			−60.4		67.3			−147.6
	83.1	−179.9	−68.5	160.8		−65.6	−32.4	−47.9	128.7
	86.6			−66.3		67.1			−147.8
	118.3	179.3	−66.6	138.4		−65.3	−32.3	−48.1	129.3
	−127.1			36.3		67.2			−148.2
	81.9	−175.5	−68.3	161.7		−63.5	−33.8	−49.7	139.8
H_{26}^{I}	−158.5			168.5	$H_{18/20}^{I}$	85.2			−67.2
	77.8	175.8	172.5	77.4		−94.5	64.9	−168.0	−131.6
	85.1			−71.8		87.2			−60.4
	−88.1	178.9	174.1	155.8		−123.6	60.9	−98.6	162.0
	75.8			26.9		152.9			−151.1
	91.0	−173.7	−179.5	−168.1		−87.8	76.7	−81.5	154.8
	60.6			44.6		167.9			176.1
	79.1	−180	177.2	97.3		−88.0	77.5	−84.8	168.1
H_{12}^{I}	72.3			28.8	$H_{20/18}^{I}$	148.8			−162.3
	123.4	−52.6	−62.3	124.9		−107.3	49.3	−94.5	133.8
	69.8			29.1		170.2			176.5
	123.3	−52.1	−62.7	122.6		−124.1	55.6	−86.8	138.2
	69.6			30.6		132.6			−138.8
	122.8	−53.8	−64.0	129.8		−161.4	65.6	−82.8	174.0
	84.2			14.7		106.6			−174.4
	100.7	−68.3	−75.1	99.3		−146.5	63.3	−73.1	147.1
$H_{15/17}^{I}$	75.1			21.7					
	65.7	58.6	−147.9	170.8					
	73.2			24.1					
	69.9	60.6	−149.2	167.2					
	71.5			25.2					
	73.3	63.7	−158.2	161.4					
	80.1			11.7					
	91.8	59.5	169.2	175.4					

[a] In degrees; see structure formula **1** in Figure 1. [b] See Table 1.

conformers will change into a few rather stable conformers, which will determine the conformation dynamics. Nevertheless, the complete pool of conformers may be a good basis for a selective structure design by the introduction of substituents or backbone cyclization. Thus, backbone conformers, which are relatively unstable, could be favored over others, which were originally rather stable. A detailed look at the stabilities of the helix conformers (Tables 4 and 5 and Supporting Information) shows representatives of the mixed or β-helices most stable in both hybrid peptide classes at the HF and DFT levels of ab initio MO theory. Helices with exclusively forward or backward orientations of the hydrogen bonds are distinctly less stable. Frequently, the next stable representatives of a mixed helix group are still more stable than the most stable helix with all hydrogen bonds pointing into the same direction of the sequence (see the Supporting Information). The most stable helices of alternating α,γ- and β,γ-hybrid peptides are given in Figures 3 and 4.

The results of the PCM//HF/6-31G* calculations indicate a considerable change of the stability relationships between the various conformers in an aqueous environment (Tables 4 and 5 and the Supporting Information). This was also found in other foldamer classes[3j,8g] and can well be explained by the considerable loss of stability of the mixed helices relative to the helix types with exclusively forward or backward directions of the hydrogen bonds due to their distinctly smaller total dipole moments. In a polar medium, the helices H_{12}^{I} of the α,γ-hybrid peptides and H_{11}^{I} of the β,γ-hybrid peptides are more stable than the most stable mixed helices $H_{18/20}^{I}$ and $H_{20/22}^{I}$. Nonetheless, especially in the β,γ-hybrid peptide series, some mixed helices keep a considerable stability also in a polar environment and represent competitive folding patterns.

Even if the focus of this work is on the helix formation by interactions between non-nearest neighbor peptide bonds, the competitive possibility of interactions between neighboring peptide bonds has to be taken into account for secondary

TABLE 3. Backbone Torsion Angles[a] of the Most Stable Helices of Alternating β,γ-Hybrid Peptide Octamers at the HF/6-31G* Level of ab Initio MO Theory

helix[b]	φ	θ	ζ	ψ	helix[b]	φ	θ	ζ	ψ
H_{11}^{I}	−136.8	−72.6		130.5	H_{22}^{I}	135.1	−163.3		−113.5
	74.9	72.7	−64.8	114.4		−117.0	51.0	57.8	−154.6
	165.3	−61.6		146.9		−162.2	176.6		167.4
	71.8	68.6	−64.6	120.6		−128.8	50.1	53.6	−142.7
	160.0	−60.4		147.9		−126.2	179.2		161.6
	72.4	67.7	−65.2	122.7		−160.0	51.1	53.4	−150.8
	159.3	−62.1		155.6		−91.1	178.4		154.0
	74.3	62.1	−75.5	146.2		178.6	61.6	66.7	−155.9
$H_{15/16}^{I}$	−90.4	−164.7		120.5	$H_{11/13}^{I}$	78.8	60.7		−107.2
	83.5	60.3	−84.3	141.5		−99.2	92.8	−77.5	156.0
	162.2	−78.1		145.8		92.2	61.6		−107.4
	82.2	62.2	−81.6	142.3		−102.4	94.1	−75.3	153.4
	149.3	−76.2		150.5		92.5	62.0		−107.4
	90.3	56.3	−88.7	129.2		−104.3	95.7	−74.2	152.9
	177.0	−73.1		142.5		91.0	62.3		−109.1
	78.4	63.1	−73.4	137.7		−87.0	80.4	−83.5	156.4
H_{20}^{I}	164.1	−68.1		132.3	$H_{13/11}^{I}$	60.8	47.6		−149.6
	84.8	63.6	177.0	−164.7		−69.7	−35.0	−54.5	131.0
	155.1	−64.6		125.1		113.0	−67.8		−82.1
	82.5	61.9	179.4	−141.8		−72.1	−38.8	−51.2	133.9
	132.9	−62.3		122.7		114.5	−66.8		−82.1
	87.7	67.2	−174.8	−147.4		−72.8	−38.6	−51.6	136.1
	122.3	−59.7		133.2		117.1	−68.1		−89.5
	80.9	63.9	−178.3	−119.6		−69.6	−33.8	−49.7	152.5
H_{13}^{I}	69.3	−101.0		141.9	$H_{20/22}^{I}$	59.8	48.1		−108.2
	130.1	−60.7	−62.8	129.6		−96.8	178.5	169.7	141.3
	97.4	−91.9		113.8		59.1	51.8		−111.2
	123.1	−58.8	−62.4	134.4		−111.0	−177.8	173.9	114.2
	94.0	−93.2		112.6		77.8	59.5		−151.8
	129.9	−61.4	−61.9	128.0		−87.6	−177.9	175.4	118.8
	95.7	−90.2		119.2		82.6	62.3		−166.0
	116.7	−60.7	−61.6	136.1		−103.1	64.0	179.8	−133.7
$H_{18/17}^{I}$	−112.8	80.0		−123.9	$H_{22/20}^{I}$	75.1	53.2		−159.3
	−107.2	59.9	71.9	−151.9		−85.8	178.3	172.3	65.9
	−147.8	88.3		−153.3		72.5	59.8		−175.5
	−120.5	59.6	56.3	−143.4		−89.2	−177.6	168.9	80.6
	−142.1	155.4		−150.9		66.4	57.1		−143.0
	−132.7	53.9	54.4	−132.7		−133.8	179.8	177.0	106.5
	170.7	166.1		−113.0		52.7	47.8		−119.0
	−78.9	−59.3	179.3	−126.9		−166.9	178.3	−178.0	132.4

[a] In degrees; see structure formula **3** in Figure 1. [b] See Table 1.

TABLE 4. Relative Energies[a] of the Most Stable Helices of Alternating α,γ-Hybrid Peptide Octamers in Vacuum (HF/6-31G*, B3LYP/6-31G*) and in an Aqueous Environment (PCM//HF/6-31G*)

	ΔE		
helix[b]	HF/6-31G*	B3LYP/6-31G*	PCM//HF/6-31G*[c]
H_{10}^{I}	74.6	88.2	38.7
H_{18}^{I}	74.9	86.5	76.8
$H_{21/23}^{I}$	106.8	133.6	46.9
H_{26}^{I}	79.9	115.5	60.6
H_{12}^{I}	35.9	54.6	**0.0**[d]
$H_{15/17}^{I}$	75.9	103.2	31.5
H_{20}^{I}	75.9	94.7	67.1
$H_{10/12}^{I}$	32.1	40.9	34.9
$H_{12/10}^{I}$	4.6	21.5	31.1
$H_{18/20}^{I}$	**0.0**[e]	**0.0**[f]	52.7
$H_{20/18}^{I}$	9.2	10.5	56.2

[a] In kJ/mol. [b] See Table 1. [c] $\epsilon = 78.4$. [d] $E_T = -2213.854989$ au. [e] $E_T = -2213.868493$ au. [f] $E_T = -2227.195474$ au.

TABLE 5. Relative Energies[a] of the Most Stable Helices of Alternating β,γ-Hybrid Peptide Octamers in Vacuum (HF/6-31G*, B3LYP/6-31G*) and in an Aqueous Environment (PCM//HF/6-31G*)

	ΔE		
helix[b]	HF/6-31G*	B3LYP/6-31G*	PCM//HF/6-31G*[c]
H_{11}^{I}	52.4	50.6	**0.0**[d]
$H_{15/16}^{I}$	86.9	88.4	26.4
H_{20}^{I}	108.5	115.7	21.2
H_{13}^{I}	59.4	44.7	20.5
$H_{18/17}^{I}$	101.1	96.1	46.7
H_{22}^{I}	132.3	133.6	55.4
$H_{11/13}^{I}$	13.8	2.7	15.1
$H_{13/11}^{I}$	42.1	34.7	44.3
$H_{20/22}^{I}$	**0.0**[e]	**0.0**[f]	19.2
$H_{22/20}^{I}$	23.8	26.3	33.9

[a] In kJ/mol. [b] See Table 1. [c] $\epsilon = 78.4$. [d] $E_T = -2369.987620$ au. [e] $E_T = -2370.020399$ au. [f] $E_T = -2384.457246$ au.

structure formation. In the alternating α,γ-hybrid peptides, 9-, 7-, and 5-membered pseudocycles could result from interactions between adjacent peptide bonds. The systematic search for periodic structures of this type provides several representatives. Most stable are periodic structures with alternating 7- and 9- or 5- and 7-membered rings. Structures with only 5-, 7-, or 9-membered pseudocycles are rather unstable. The stability of the most stable conformers is comparable with that of the most stable helices with forward or backward hydrogen-bond orientations formed by non-nearest neighbor interactions but is lesser than that of the β-helices. In the β,γ-hybrid peptides, structures with 8- and 9-membered or 6- and 7-membered rings are thinkable. However, these structures are distinctly less stable

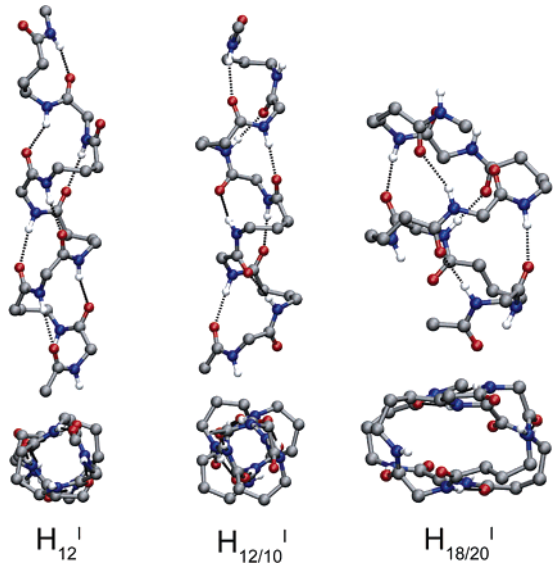

FIGURE 3. Most stable helices in blocked octamers of alternating α,γ-hybrid peptides.

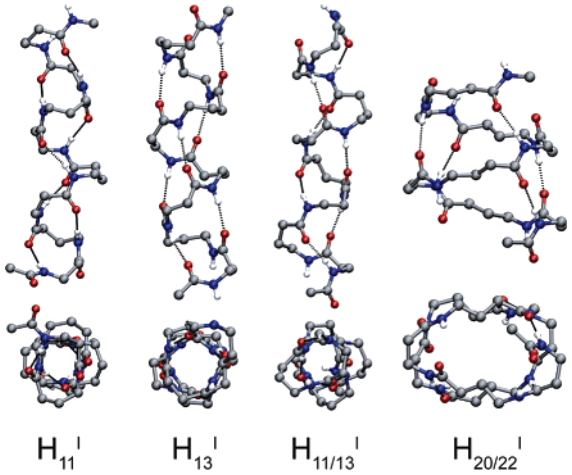

FIGURE 4. Most stable helices in blocked octamers of alternating β,γ-hybrid peptides.

than the helices resulting from the non-nearest neighbor peptide bond interactions. In the Supporting Information, structural details of these folding alternatives are available as pdb files together with the stability data for comparison. In this study, we confine ourselves to secondary structure formation by intramolecular hydrogen bonding. The possibility of secondary structure formation via intermolecular hydrogen bonding between various strands, as it is realized in the β-sheet structures of native α-peptides, has also to be considered as an alternative to helix formation in homologous peptides.[13] However, structure investigations on several peptide foldamer classes show that the extension of the amino acid backbones leads to a preference of gauche conformations.[3f−h] Thus, the tendency to form sheetlike networks seems to be at least decreased in foldamers of higher homologous amino acids.

Relationships between α,γ- and β,γ-Hybrid Peptide Helices and Helices in β- and α-Peptides. It is well-known that a δ-amino acid constituent in a peptide sequence may approximately replace a dipeptide unit in the native α-peptides.[3h,6a,14] Thus, close relationships should be expected between the overall backbone structure of α- and δ-peptides. Indeed, some similarities, but also characteristic differences, can be observed in the helix and β-turn formation of α- and δ-peptides.[3h] Most important is the loss of a peptide bond by introduction of a δ-amino acid constituent, which could have consequences for the interaction behavior. Similar relationships could be expected when comparing the basic dipeptide units of the α,γ-hybrid peptides with that of β-peptide sequences and when comparing β,γ-dimers with α-peptide trimers (Figure 1).[6] Thus, a dimer unit of the α,γ-hybrid peptides may formally replace a dipeptide unit in β-peptides, and the dimer unit of the β,γ-hybrid peptides corresponds to a tripeptide unit in the native α-peptides. It may be interesting to see whether the shape and the stability of the corresponding helix types correlate in the two peptide classes.

In the α,γ-hybrid peptides, the helix H_{12}^{I} with all hydrogen bonds in backward direction is the most stable helix in an aqueous medium. It finds its counterpart in the experimentally confirmed H_{12} helix of β-peptides,[15] which belongs to the most stable secondary structures there.[3e,j] The overlay of both structures in Figure 5a demonstrates the close relationship between the overall topologies of the two helices with an RMSD value of 0.6 Å for the comparison of the corresponding basic units according to Figure 1 despite the shift of one peptide bond. Structural similarities exists also between various mixed helices of the two peptide classes. The β-helices of the $H_{12/10}$ type and the helix conformers with the next larger sizes of the alternating hydrogen-bonded rings, $H_{18/20}$, belong to the most favorite structures both in α,γ-hybrid peptides and in β-peptides, where the $H_{12/10}$ helix type was experimentally found.[8c,d] The superimposition of the β-helix $H_{12/10}^{I}$ of the α,γ-hybrid peptides and the experimentally confirmed $H_{12/10}$ helix of the β-peptides in Figure 5b provides an RMSD value of 0.7 Å. Helices with hydrogen bonds in the forward direction are generally rather unstable in α,γ-peptides. Here, a correspondence between the most stable H_{10}^{I} conformer and H_{10} helices, as they are discussed for β-peptides,[3e,16] could be expected. The structure of the well-known H_{14} helix in β-peptides[17] can not a priori be realized in the α,γ-hybrid peptides.

The comparison between β,γ-hybrid peptides and secondary structures of the native α-peptides provides similar agreements.

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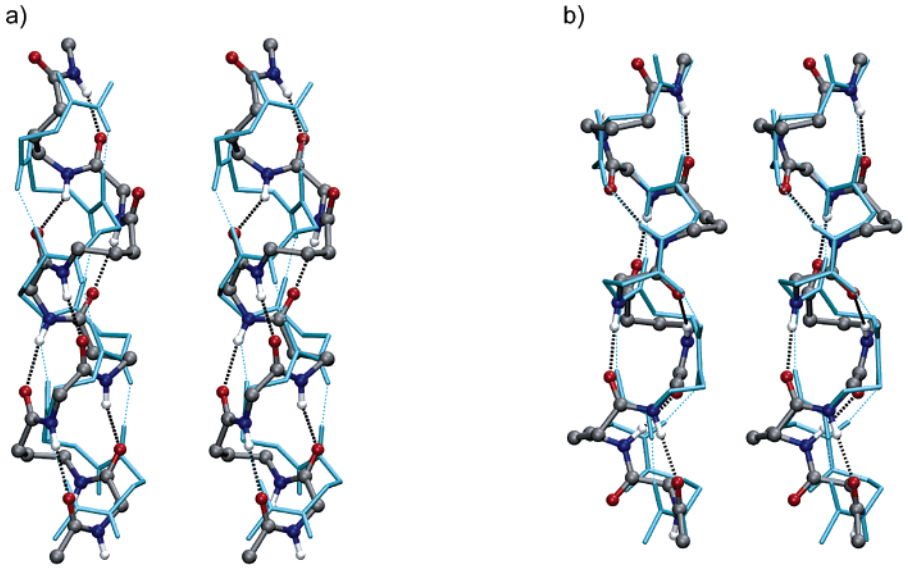

FIGURE 5. (a) Stereoview of the superimposition of the most stable helix of α,γ-hybrid peptides in an aqueous environment, H_{12}^{I}, and the experimentally confirmed H_{12} conformer in β-peptides. (b) Stereoview of the superimposition of the most stable mixed helix $H_{12/10}^{I}$ of the α,γ-hybrid peptides and the experimentally found $H_{12/10}$ helix of the β-peptides (reference structures in light blue).

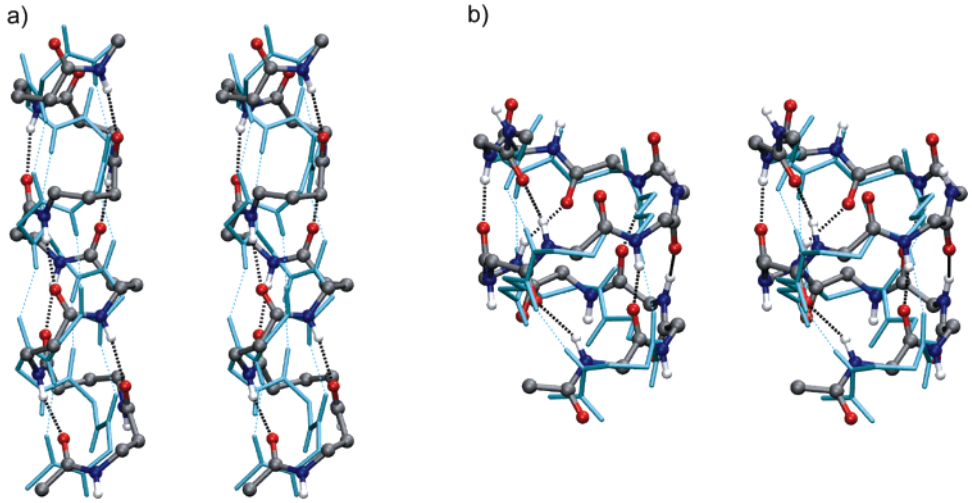

FIGURE 6. (a) Stereoview of the superimposition of the helix H_{13}^{I} of the β,γ-hybrid peptides and an α-helix dodecamer. (b) Stereoview of the superimposition of the most stable mixed helix $H_{20/22}^{I}$ of the β,γ-hybrid peptides and the gramicidin A membrane channel (reference structures in light blue).

Of particular interest are the helices of the H_{13} group, since they correspond formally to the well-known α-helix of native peptides and proteins. In fact, the superimposition of the rather stable H_{13}^{I} conformer of the β,γ-hybrid peptides with backward orientation of the hydrogen bonds and an α-helix octamer in Figure 6a demonstrates a very good correspondence between the two helix patterns with an RMSD value of 0.7 Å for the comparison of the corresponding basic units according to Figure 1. The H_{13}^{I} helix of the β,γ-hybrid peptides exhibits the same directions of the helix dipole and the hydrogen bond orientations as the α-helix. This is a hint that β,γ-peptide units might well adopt the α-helix conformation in native peptide sequences despite the different number and positions of the peptide bonds in the basic units of the two peptide classes.

A further interesting parallelism concerns the mixed helices of the types $H_{20/22}$ and $H_{22/20}$. $H_{20/22}^{I}$ is the most stable helix type of the β,γ-hybrid peptides at the HF and DFT levels of ab initio MO theory and remains rather stable in polar media. This structure could well be compared with the structure of the gramicidin A membrane channel.[18] The gramicidin A peptide is alternately composed of D- and L-α-amino acids and represents a $H_{20/22}$ β-helix of an α-peptide sequence. The overlay of the two structures in Figure 6b with an RMSD value of 0.6 Å supports again the suggested correspondence of the secondary structure formation in hybrid peptides and peptide sequences exclusively composed of a single type of homologous amino acids. This is especially surprising for the mixed helices of β,γ-peptides, since the blocked dimer unit with one central peptide bond mimics an α-amino acid trimer with two central peptide bonds (Figure 1). Thus, the backward/forward alternation of the hydrogen bonds in the comparable mixed helices of β,γ-hybrid

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peptides and α-peptides shows a shift. Nonetheless, the resulting overall topologies are completely analogous (Figure 6).

The H_{11}^{I} helix of the *β*. *γ*-hybrid peptides, which is predicted to be most stable in an aqueous medium, deserves some attention for structure design since it opens up the possibility for helices with the backbone correspondence to α-peptides, but an orientation of the hydrogen bonds in forward direction, which was not found in native α-peptides until now.

Conclusions

The results of our systematic conformational analysis indicate that alternating α,*γ*- and *β*,*γ*-hybrid peptides are promising novel classes of peptide foldamers. They are able to form various stable helical structures with interesting types of hydrogen-bonding patterns. In an apolar environment, representatives of mixed or *β*-helices with alternating directions of the hydrogen bonds are most stable. In a more polar environment, this situation changes in favor of helix types with the same direction of all hydrogen bonds. Special structural aspects of secondary structure formation result from the backbone correspondence between alternating α,*γ*- and *β*,*γ*-hybrid peptides and dipeptide and trimer units of *β*- and native α-peptides, respectively. Thus, there are close relationships between the most stable helices of the hybrid peptides and those of peptides that are exclusively composed of a single type of homologous amino acids. The pool of obtained helices represents a good basis for a selective secondary structure design by the introduction of backbone substituents or backbone cyclization. Thus, the two novel hybrid peptide classes are especially interesting as tools for mimicking native peptide and protein structures and may stimulate synthetic work in this field.

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Supporting Information Available: Tables with the backbone torsion angles of the α,*γ*- and *β*,*γ*-hybrid peptide octamers at the B3LYP/6-31G* level of ab initio MO theory, with the total energies of all 101 helical conformers at the HF/6-31G*, B3LYP/6-31G*, and PCM//HF/6-31G* levels of ab initio MO theory, with the backbone torsion angles and stabilities of secondary structures with interactions between nearest neighbor peptide bonds, and pdb files for all 101 helix octamers and the periodic structures with interactions between nearest neighbor peptide bond interactions on the basis of the HF/6-31G* geometries. This material is available free of charge via the Internet at http://pubs.acs.org.

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