β-Peptides: From Structure to Function

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Contents

I. Introduction

In recent years, our understanding of protein structure and function has advanced rapidly, providing a mechanistic understanding of a wide variety of biological processes. As an outgrowth of this understanding, chemists are now beginning to design and redesign proteins with impressive results (see other papers in this issue and ref 1). It is important now to ask whether this understanding represents a true comprehension of the underlying molecular phenomena or if it is idiosynchratic to the specific geometries and characteristics of proteins composed of the commonly occurring amino acids. If our understanding is general, it should be possible to design biomimetic polymers that show both secondary and tertiary structures analogous to those of natural proteins. Nature herself suggests that such biomimetic polymers are reasonable targets, because RNA, like proteins, can adopt characteristic secondary and tertiary structures. Dill and co-workers suggested that specific secondary and tertiary folding might be widespread among heteropolymers with certain sequence characteristics.[2] In RNA, as in proteins, specific folding underlies diverse informational and catalytic functions, even though proteins and RNA have very different backbones. Thus, it should be possible for the chemist to design functional polymers with biological, catalytic, and organizational properties not precedented in nature.

In the past decade, increasing work has been devoted to the study of homogeneous, sequence-specific oligomers that mimic various aspects of the folding and organization of polypeptides.[3−5] The pioneering work of Dervan and co-workers on DNA-binding aromatic polyamides based on pyroles and imidazoles predates this era and provides a glimpse of what can be accomplished through a sustained multidisciplinary approach to the problem of oligomer design;[6,7] using this approach it is now possible to design molecules that target a variety of nucleotide sequences by making sequence-specific contacts in the minor groove. More recently, Hamilton and co-workers examined the design and folding of various other aromatic polyamides,[8−10] which, like the polypyrrole and poly-imidazole carboxamides, are relatively rigid and capable of adopting well-defined structures. Foldamers other than aromatic polyamides have also been explored, including nucleic acids with alternative sugar[11−13] and peptidic[14−17] backbones and completely nonnatural constructs such as aedamers[18] and oligo(phenylene-ethynylenes).[19] Other workers have focused on structures that more closely resemble conventional peptides including peptoids,[20−23] β-peptides,[3,24−26] γ-peptides,[27,28] and others.[29−38]

β-Peptides have particular appeal for extending our understanding of protein structure and stabilization into the realm of folded, nonbiological polymers, because β-amino acids represent the smallest step away from α-amino acids in "backbone space". Like α-peptides (i.e., peptides composed of α-amino acids), β-peptides contain amide bonds capable of forming stabilizing, intramolecular hydrogen bonds. A large body of structural and synthetic work has laid a solid groundwork for current investigations into β-peptides. For example, C^3-substituted β-amino acid may be prepared by homologation of α-amino acids[39] or by a number of other practical routes,[40−43] providing

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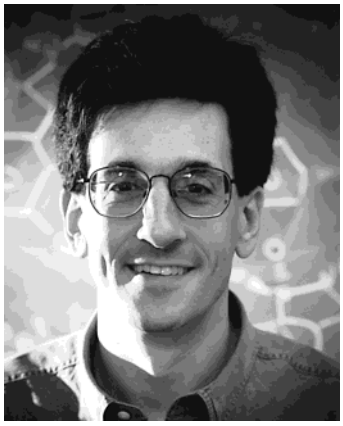
Richard P. Cheng was born in St. Louis, MO. After obtaining his B.S. degree in Chemistry from National Taiwan University in 1992, he earned his Ph.D. degree in Chemistry at the California Institute of Technology in 1998 under the guidance of Barbara Imperiali and co-advisor Harry B. Gray. His postdoctoral research with William F. DeGrado and Mark A. Scialdone started at DuPont and has continued in the Department of Biochemistry and Biophysics at the University of Pennsylvania.



Samuel H. Gellman earned his A.B. degree in Chemistry from Harvard University in 1981 and his Ph.D. degree from Columbia in 1986. In 1987, after 18 months of postdoctoral research at the California Institute of Technology, Gellman moved to the University of Wisconsin at Madison, where he is currently the Evan P. Helfaer Professor of Chemistry.

a convenient and highly diverse source of monomers.

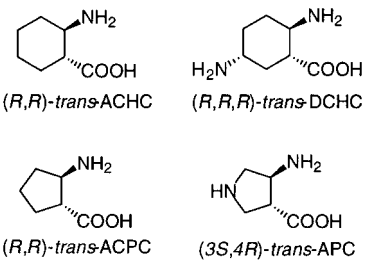
Early investigations of polymeric β-peptides indicated that they were able to adopt stable helical structures, although the precise helix geometries have been challenging to elucidate.[44−48] Sheet secondary structures have also been proposed for β-amino acid polymers.[49−52] Finally, there have been extensive studies of the structures of cyclic peptides containing β-amino acids.[53−63] These investigations, which are beyond the scope of this review, helped to elucidate the low-energy conformations of β-peptides and provided a solid framework for contemporary studies of β-peptides.

II. Conformational Properties of β-Amino Acids

The conformations of β-peptides can be analyzed in terms of the main chain torsional angles, which are assigned the angles ω, ϕ, θ, and ψ (Figure 1) in the convention of Balaram.[62] Folded helical or turn-like conformations of β-peptides require a gauche conformation about the θ torsion angle defined by the C^2-C^3 bond. A trans rotamer leads to a fully extended conformation, provided the values of ϕ and ψ are appropriate. The effects of substituents on the conformation of β-amino acids have been the subject of extensive experimental studies[39,64−67] as well as molecular orbital[68−70] and molecular mechanics/dynamics calculations.[71−80] Wu and Wang carried out an interesting comparison of various molecular mechanics force fields versus ab initio calculations and found reasonably good general agreement among the methods.[68]

William F. DeGrado received his Ph.D. degree in Organic Chemistry with E. Thomas Kaiser from the University of Chicago (1981), was a member of the scientific staff of DuPont and DuPont-Merk Pharmaceutical Company from 1981 to 1996, and is currently the George W. Raiziss Professor of Biochemistry and Biophysics in the Department of Biochemistry and Biophysics, University of Pennsylvania.

The effects of substituents on the local conformation of a β-amino acid are summarized in Figure 2. The unsubstituted β-amino acid, β-alanine, is highly flexible, analogous to Gly in the α-amino acids. Alkyl substituents at positions 2 and 3 favor a gauche conformation about the C^2-C^3 bond.[39] C^2,C^3-Disubstituted amino acids are even more conformationally constrained and favor gauche conformers when the substituents are anti (aldol convention). Gauche-type torsion angles are even more strongly promoted when these atoms are included in a cyclohexane or cyclopentane ring, as in *trans*-2-aminocyclohexanecarboxylic acid (ACHC),[76,81] *trans*-2,5-diaminocyclohexanecarboxylic acid (DCHC),[82,83] *trans*-2-aminocyclopentanecarboxylic acid (ACPC),[77,84] or *trans*-3-amino-pyrrolidine-4-carboxylic acid (APC).[85] The ring size determines the precise C^2-C^3 torsional preference, which in turn influences β-peptide helix type.[77]



When substituents at C^2 and C^3 are syn, a trans conformation about the C^2-C^3 bond is favored, which encourages the formation of sheetlike structures.[39,67,86] It is interesting to consider $C^{2,2}$- and $C^{3,3}$-disubstituted β-amino acids in light of the well-known

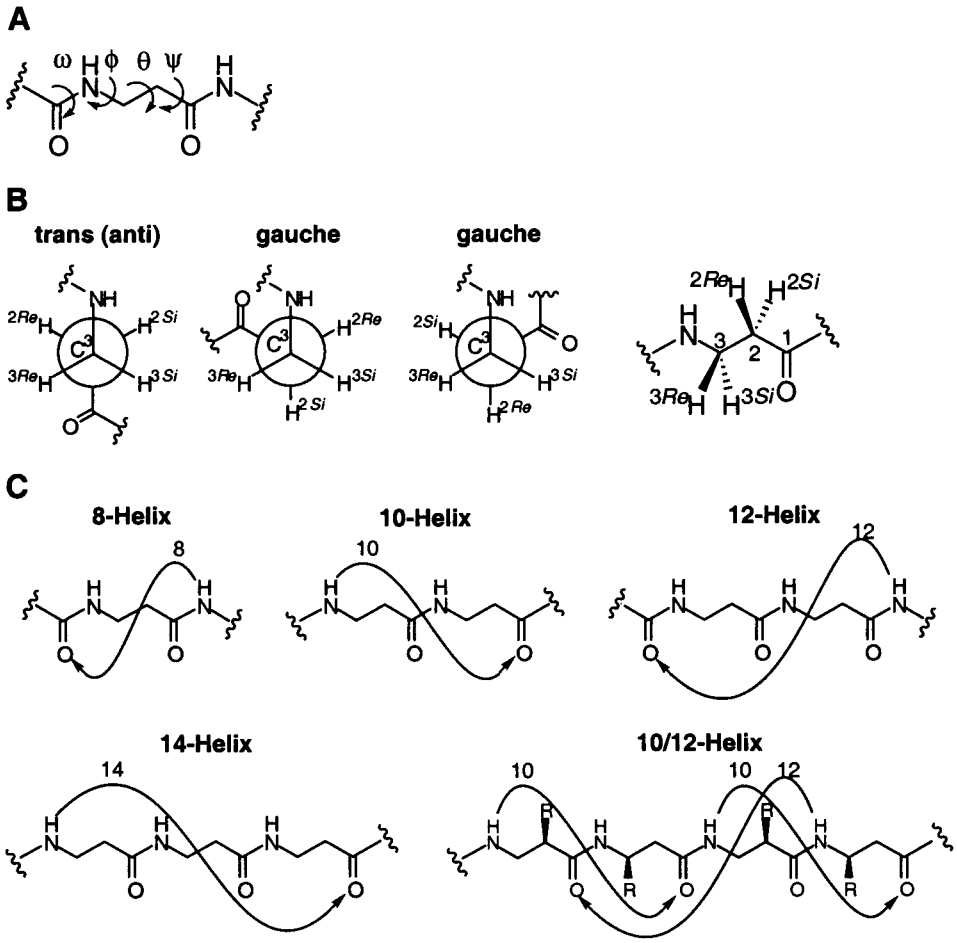


Figure 1. (A) Definition for the torsional angles in β-peptides. (B) Rotamers for β-alanine regarding the θ dihedral. (C) Nomenclature for β-peptide helices based on hydrogen-bonding patterns.

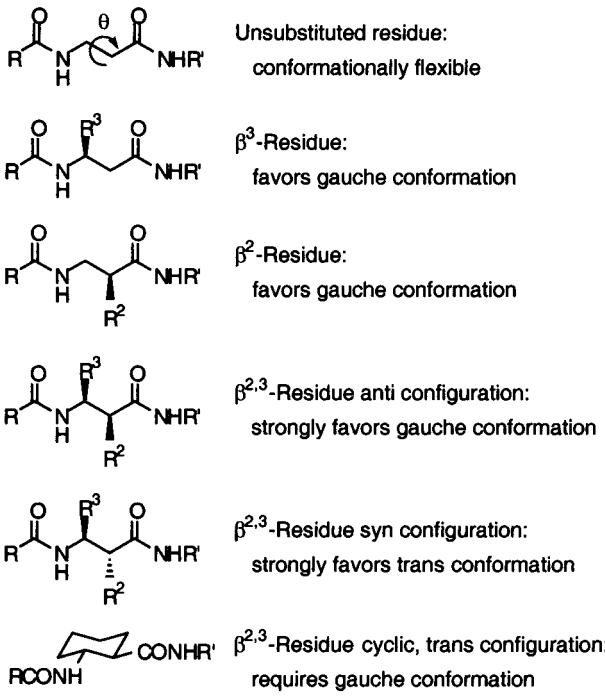
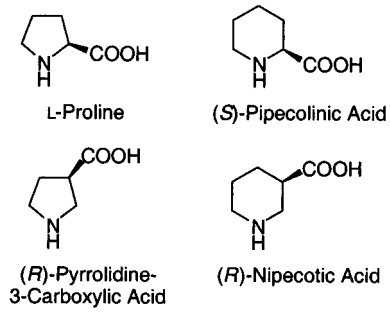


Figure 2. Effect of substituents on the torsional angle, θ.

tendency of dialkyl α-amino acids such as α-aminoisobutyric acid to induce helical and turn-like conformations in α-peptides.[87] In β-peptides, this constraint stabilizes reverse turns.[88,89]



The cyclic amino acids pyrrolidine-3-carboxylic acid (Pca) and nipecotic acid (Nip) are β-substituted equivalents of Pro and pipecolinic acid, respectively, and hence, their conformational properties may be similar to those of the corresponding α-amino acids.[90,91] Because of their cyclic nature, one might expect Pca and Nip to be relatively rigid and to break helices that require hydrogen bonding between amide NH protons and backbone carbonyls. Indeed, as is the case for short Pro sequences, short homochiral peptides composed of Pca and Nip[92] appear to adopt well-defined conformations based on circular dichroism spectroscopy (CD).[93] Also, as discussed below, heterochiral dipeptide sequences incorporating Nip (e.g., *S*-Nip-*R*-Nip) strongly stabilize reverse turn formation[66,94,95] in a manner analogous to the stabilization of reverse turns by heterochiral Pro-containing dipeptides.[90,96−101]

Table 1. Nomenclatures for *β*-Peptide Helices

Applequist[a]	Subirana[b]	Gellman[c]	Seebach[d]	helix nomenclature[e]
R_{+2}	2R	14	(P) 3_1	3_{14}
R_{+3}	4R	18		
R_{-3}		12	(P) 2.5_1	2.5_{12}
R_{-4}	1R	16		
R_{-5}	3R	20		
L_{+2}	2L	14	(M) 3_1	3_{14}
L_{+3}	4L	18		
L_{-3}		12	(M) 2.5_1	2.5_{12}
L_{-4}	1L	16		
L_{-5}	3L	20		

[a] The nomenclature describing the helix handedness and hydrogen-bonding patterns between hydrogen-bond donor and acceptor atoms; $R_{\pm n}$ denotes a right-handed helix in which NH_i is hydrogen bonded to $CO_{i\pm n}$, and $L_{\pm n}$ denotes a left-handed helix with the same hydrogen-bonding pattern. [b] The nomenclature[47] describing the hydrogen-bonding patterns; R and L designate right- and left-handed helical topologies, respectively. [c] A nomenclature describing the number of atoms comprising the hydrogen-bonded ring formed between donor and acceptor atoms.[76,77] [d] Seebach's nomenclature describes the helical symmetry; P and M refer to right- and left-handed helical topologies, respectively.[103] [e] The nomenclature provides the number of residues contained in one helical turn; the subscript denotes the number of atoms comprising the hydrogen-bonded ring formed between donor and acceptor atoms.

III. Helical Conformations

Polyamide sequences composed of C^2- and/or C^3-substituted *β*-amino acids adopt helical conformations—the nomenclature for which has varied widely in the literature (Table 1[47,76,77,103]). Here, we adopt a convention (Figure 2) that depends on the number of atoms in the hydrogen-bonded ring.[76,77] Other conventions for naming the helical forms of *β*-peptides are summarized in Table 1. Naming the helices based on the number of atoms in the hydrogen-bonded rings is advantageous since the name provides some structural information, but the names are not so precise as to risk becoming misnomers. Among α-helices, variation from the ideal structure is common[102] and one observes a continuum of states ranging from the 3_{10}-helix to the *π*-helix. In addition, alternative helix nomenclatures cannot easily handle less symmetrical structures such as the 10/12-helix.

A. 14-Helix

Fiber diffraction and IR (infrared) investigations of poly(α-isobutyl-L-aspartate) provided an early indication that *β*-peptides are able to form helical structures, including the 14-helical conformation.[45−48] However, interpretation of the polymer data was not completely straightforward, and a variety of helix and sheet conformations were proposed.[45−48,52] More recently, the synthesis of *β*-peptides of defined sequence has enabled high-resolution structural studies of this class of compounds. NMR (nuclear magnetic resonance) and crystallographic studies of *β*-peptides containing the conformationally constrained cyclic amino acid *trans*-2-aminocyclohexanecarboxylic acid (ACHC) have shown that these peptides adopt 14-helices in the solid state as well as in organic solvents.[76,83] Seebach's group found that a series of *β*-peptides prepared from acyclic residues with a diverse collection of side chains also adopts a 14-helix in organic solvents.[39,74,103,104] Depending on the stereochemistry of the *β*-amino acids, either a left-handed or a right-handed 14-helix is formed. Peptides formed from β^3-amino acids derived from naturally occurring L-amino acids adopt left-handed 14-helices.

The 14-helix (Figure 3) is stabilized by hydrogen bonding between an amide proton at position *i* and a main chain carbonyl at position *i+2*, forming a

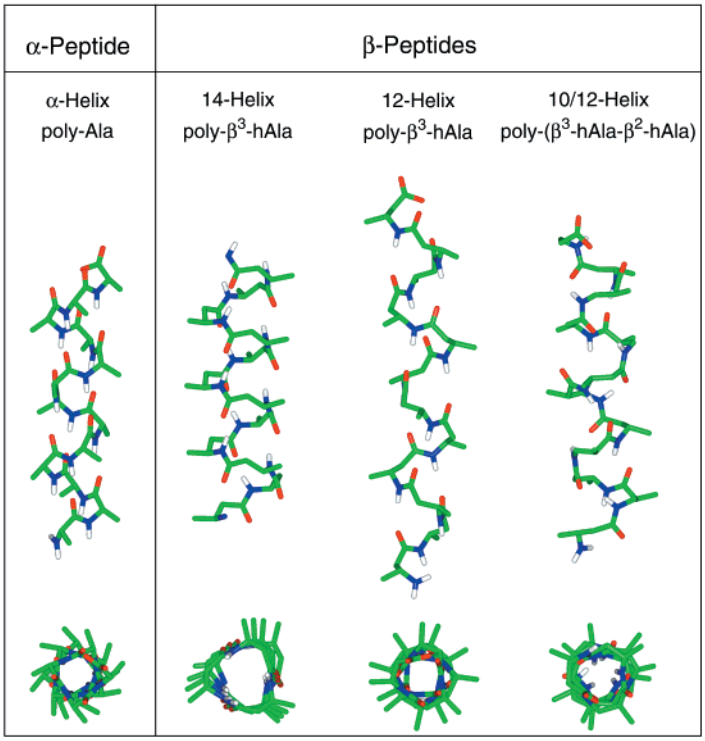


Figure 3. Structure of the α-helix, 14-helix, 12-helix, and 10/12-helix. The hydrogens are omitted for clarity, except for the amide hydrogens (white). Carbon atoms are shown in green, nitrogen in blue, and oxygen in red.

Table 2. Torsional Angles and Helical Parameters for β-Peptide Helices and α-Helix

characteristic	14-helix[79]	12-helix[84]	α-helix[105]
ϕ (°)	−134.3	95.0	−57
θ (°)	60	−94.3	
ψ (°)	−139.9	103.0	−47
ω (°)	180.0	−180.0	180
radius (Å)	2.7	2.3	2.2
residues/turn	3.0	2.5	3.6
rise/residue (Å)	1.56	2.1	1.5

series of intercatenated 14-membered rings (Figure 1C). The overall structure of the 14-helix differs from that of the α-helix in many respects. The 14-helix has a slightly wider radius and a shorter rise for a given chain length than the α-helix (Table 2[79,84,105]). The amide carbonyl and NH groups project toward the N- and C-terminus, respectively, in the 14-helix, resulting in a net dipole opposite to that of the α-helix. Further, while the α-helix has a 3.6-residue repeat, the 14-helix repeats approximately every 3 residues,[39,76,103,104] which positions the side chains of every third residue directly atop one another along one face of the helix (Figure 3).

1. CD Spectroscopy of 14-Helices

Circular dichroism (CD) spectroscopy has provided a very rapid and quantitative method to examine the structure and conformational changes of α-helical peptides. This method should be similarly useful for the study of the 14-helix. The CD spectra of several hexa- and heptapeptides, which adopt left-handed 14-helices as determined by NMR or crystallography, show a maximum near 195 nm and a minimum near 215 nm (or vice versa for right-handed helices). The magnitude of the negative ellipticity at 215 nm varies somewhat from peptide to peptide.[39,74,81,103,104,106] However, it is possible that some or all of these peptides are not fully helical. NMR spectroscopy would not be sensitive to a small amount of non-helical structure, so long as it was in rapid exchange with the primary conformation. Consistent with this suggestion, the ellipticity is greatest for those peptides with the most conformationally restricted amino acids, which lead to minimal fraying of the ends of the helices. The magnitude of the mean residue ellipticity at 215 nm for these peptides approaches approximately (2×10^4) deg cm^2 dmol^{-1}.[39,81,106]

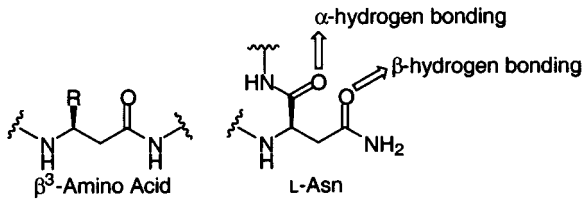
The contribution of the $\pi-\pi^*$ transition to the CD spectrum of the 14-helix has been calculated by Bode and Applequist.[79] Because of excitonic coupling, this transition is split into two orthogonally polarized bands at 194 and 204 nm. The higher energy band is in good agreement with experiment. The observed value of 214 nm for the lower energy band probably reflects the presence of an overlapping $n-\pi^*$ transition, centered at a slightly longer wavelength. Studies with oriented samples[107,108] would allow one to address the origins of the spectrum in greater detail.

The intensity of the CD spectrum of the α-helix is known to depend on chain length, becoming more intense as the helix is lengthened.[109,110] Similar behavior appears to be found for 14-helices. The CD spectra of many 10−15-residue peptides, which have been designed to adopt a 14-helical conformation, are more intense than their shorter counterparts.[106,111] For example, the ellipticities of a series of amphiphilic β-peptides have been examined in the presence of micelles, which strongly stabilizes the 14-helical conformation. Their mean residue ellipticities increase in a length-dependent manner, and the intensity of the band at 215 nm approaches a value of approximately −28 000 deg cm^2 dmol^{-1} at a chain length of approximately 15 residues.[111] Thus, this value provides a possible limit for the mean residue ellipticity of a long, left-handed 14-helix. However, this conclusion should be tempered by the fact that the longer β-peptides were not structurally characterized by methods other than CD and that the longest β-peptide to be structurally characterized by NMR or X-ray crystallography is only eight residues in length.[77,106]

In summary, CD spectroscopy has proven to be a very useful qualitative tool for assessing the presence of the 14-helix in β-peptides. As the structural database of longer 14-helical peptides increases, it should be increasingly possible to use CD as a quantitative tool for measuring thermodynamic transitions in a manner analogous to its use for studying such transitions in proteins and α-helical peptides.[112] However, as is the case for α-peptides, it is less likely to be as useful for determining the presence of less regular conformations that lack intense bands arising from coupling of closely interacting amides.

2. Thermodynamic Stabilization of the 14-Helix

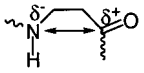
It is interesting to consider the conformational stability of β-amino acids in light of the well-studied conformational properties of the α-amino acids. Of particular interest are the C^3-monosubstituted β-amino acids (i.e., β^3-amino acids), which differ from the commonly occurring α-amino acids by the insertion of a single methylene group. One might expect that the insertion of an unsubstituted methylene group would increase the conformational flexibility of the β-amino acids, resulting in a more unfavorable entropy associated with helix formation.[25,104,113] However, an opposing view is reached by considering the conformational behavior of Asn, the only β-amino acid amide among the commonly occurring α-amino acids.



In protein structures, Asn may form intramolecular hydrogen bonds with either its β-carbonyl and/or its α-carbonyl (designated β- and α-hydrogen bonding, respectively). If Asn is added to the N-terminus of a preformed helix, these two possibilities are generally mutually exclusive[114−118] and hydrogen bonding via the α-carbonyl extends the helix, while the formation of hydrogen bonding with the β-carbonyl results in helix termination via an "N-capping" interaction. The N-capping interaction is favored relative to helix extension by approximately 1.0−2.0 kcal/mol.[112,119,120]

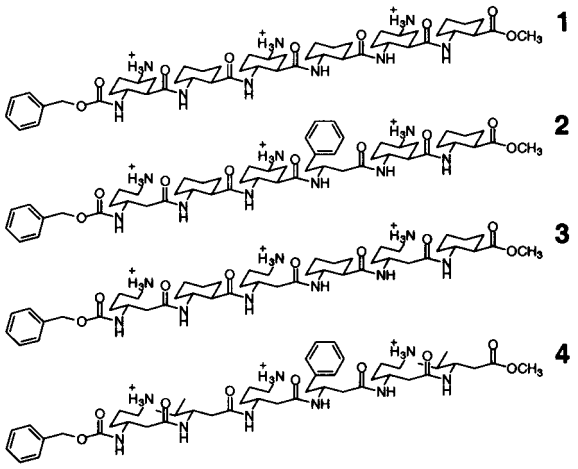
Thus, in the proper context such as N-capping, the energetics of β-hydrogen bonding, which requires the restriction of three dihedral angles, can be energetically more favorable than α-hydrogen bonding, which restricts only two torsions. Thus, it might be expected that β-peptides would form stable, intramolecularly hydrogen-bonded structures.

Consistent with this expectation, in organic solvents the 14-helix conformation is quite stable relative to the α−helical conformation of α-peptides. Helix formation in biopolymers is generally length-dependent, with significant helix formation occurring only after a critical chain length is reached. In organic solvents such as methanol or trifluoroethanol, α-peptides composed of natural amino acids require approximately 10−12 residues to form stable helices; by contrast, 14-helices are formed in β-peptides composed of β^3-monosubstituted amino acids with as few as six residues.[39,103,104] Further, highly conformationally constrained β-peptides can form helices with even four residues.[106] These peptides include sequences consisting of conformationally restricted amino acids, such as the cyclohexane-containing ACHC, as well as sequences composed exclusively of more flexible C^2- or C^3-monosubstituted β-amino acids. Wu and Wang proposed that the enhanced stability of the 14-helix conformation by β-amino acids in organic solvents may arise from an electrostatic interaction between the partial charges of the carbonyl carbon and the amide nitrogen,[68] which preferentially stabilizes a gauche conformation, as required for 14-helix formation.



The effects of substituents on the formation of the 14-helix have been extensively studied. Substitution patterns that favor the formation of a gauche conformation about the C^2-C^3 bond (Figure 2)—such as monosubstitution at C^2 or C^3—favor 14-helix formation. The inclusion of the C^2-C^3 bond within a cyclohexane ring (as in trans-ACHC) is a particularly strong conformational restraint,[76] which locks the θ angle to approximately ±55°. By contrast, *syn*-C^2,C^3-disubstitution favors a value of θ near 180° and hence strongly destabilizes helix formation. Also, disubstitution at either C2 or C3 sterically prevents 14-helix formation, because this conformation forces one of the two alkyl groups into an axial position proximal to the helical axis.[103]

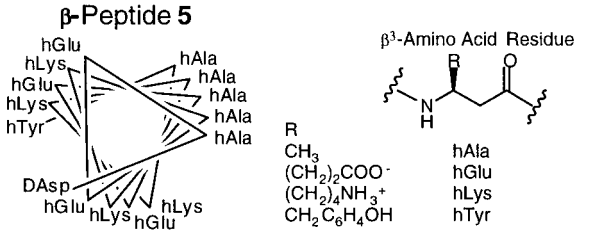
As is the case for α-helices, the 14-helix conformation is generally much less stable in water than in organic solvents. For example, CD and NMR investigations of a series of water-soluble β-peptides, **1**−**4**, show the importance of conformationally constrained cyclohexane-containing amino acids in stabilizing the 14-helical conformation. As the number of cyclohexane-containing amino acids decreases from six to zero in these peptides, the ellipticity at 215 nm decreases to negligible levels. Similarly, a β^3-homolysine-containing peptide appears to form a partial 14-helix conformation in methanol as assessed by CD spectroscopy but forms a more random coil-like conformation upon addition of increasing concentrations of water.[121,122] A more direct comparison between α-peptides and β-peptides may be obtained by comparing the amphiphilic peptides (Leu-Lys-Lys-Leu-Leu-Lys-Leu)$_2$ with (β^3-hLeu-β^3-hLys-β^3-hLeu)$_n$, $n = 2-6$. In both cases, the hydrophobic Leu (or β^3-hleu) and hydrophilic Lys (or β^3-hLys) residues were arranged to lie on opposite sides of an α-helix and a 14-helix, respectively, and the Leu/Lys and β^3-hLeu/β^3-hLys ratios were similar (1/3 = 0.33 for the α-peptides versus 3/7 = 0.42 for the β-peptides). The α-peptide showed a monomer−tetramer equilibrium whose equilibrium constant depended on the concentration of NaCl.[123] At low peptide concentrations and low [NaCl], the peptide was partially α-helical and monomeric, while at higher peptide concentrations and higher [NaCl], the α-peptide formed fully α-helical tetramers. By contrast, the β-peptides showed essentially no helical content as assessed by CD spectroscopy at low or high concentrations of peptide in the presence or absence of 0.15 M NaCl. Only in the presence of micelles did this series of β-peptides adopt a 14-helical conformation. Thus, in water, β^3-substituted amino acids appear to have somewhat lower intrinsic potentials to form a 14-helix as compared to the intrinsic potential of the corresponding α-peptides to form α-helices.



Examination of the structure of the α-helix versus the 14-helix suggests that medium-range interactions (between residues one turn apart in the helix) may be much more important for stabilizing the 14-helix than is the case for α-helices. For example, in the β-peptide 14-helix, the C^3 atoms of residues situated at positions *i* and *i+3* are quite close (4.8 Å) and side chains projecting from these positions are directed nearly parallel to one another (Figure 3). By contrast, in an α-helix, the C^α atoms of residues *i* and *i+4* are 6.3 Å apart and directed at a 40° angle relative to one another. In fact, neighboring side chain juxtapositions in the 14-helix are similar to those encountered in a β-sheet, in which the side chains are spaced by about 5 Å and oriented approximately parallel to one another. In this context one might expect side chain interactions between residues one turn apart to be highly context-dependent for 14-helices, similar to the β-sheet structure among conventional peptides.[124−134] For example, antiparallel β-hairpins can be stabilized by interstrand disulfides between Cys side chains.[135−141]

Similarly, disulfides between residues at positions *i* and *i+3* strongly stabilize a 14-helix.[142] Disulfides at positions *i* and *i+4* are also able to provide a weak stabilization of α-helices, although a much longer side chain is necessary, and the stereochemistry of the first residue needs to be reversed.[143]

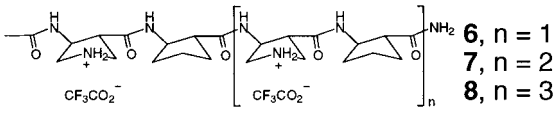
The different roles of short- versus medium-range interactions for stabilizing the 14-helix in water has recently been probed in peptides with electrostatically complementary side chains at positions *i* and *i+3*.[144,145] These peptides are analogous in composition and length to earlier monomeric α-helical peptides,[146,147] and they contain blocks of β^3-hGlu and β^3-hLys that interact across turns of the helix. For peptide **5**, a C-terminal D-Asp residue was included because this residue has been shown to stabilize 14-helix formation,[122] possibly via the formation of hydrogen bonds between its carboxylate and the exposed backbone amides at the end of the helix. On the basis of its CD spectrum, peptide **5** is nearly fully helical. Further, the 14-helical conformation is lost at low pH, where the β^3-hGlu side chains are protonated, and at high pH, where the β^3-hLys side chains are deprotonated, as well as at high salt concentrations, which effectively screen the intramolecular electrostatic interactions. This behavior contrasts with closely related α-helical peptides,[146−148] which show less complete helix formation near neutral pH and low ionic strength. Further, these α-helical peptides lose only a part of their helical content at extremes of pH and ionic strength.[146−148] Thus, as compared to α-amino acids in the α-helical conformation, β^3-amino acids appear to be intrinsically less stable in a 14-helix conformation in aqueous solution, although medium-range interactions between side chains of the β^3-amino acids can override their intrinsic preferences.



H-hTyr-hAla-hLys-hLys-hAla-hGlu-hGlu-
hAla-hLys-hLys-hAla-hGlu-hGlu-hAla-DAsp-OH

B. 12-Helix

Systematic conformational searches and molecular dynamics calculations of the cyclopentane-containing amino acid *trans*-2-amino-cyclopentanecarboxylic acid (ACPC) versus the *trans*-cyclohexyl amino acid ACHC have revealed inherent preferences for different helical conformations.[78] The cyclohexyl ring of ACHC stabilizes the θ torsional angle to a value near ±60°, which specifically stabilizes the 14-helical conformation. The smaller ring size of ACPC biases θ toward larger values, rendering a novel helical form, the 12-helix, as the most favorable helical conformer (Figures 1 and 3). The structure of the 12-helix is stabilized by a series of hydrogen bonds between amides carbonyl groups at position *i* and an amide proton at position *i+3* in sequence. The helix repeats approximately every 2.5 residues and shows the same polarity as the α-helix, with the amide protons exposed from the N-terminal end of the helix. The ability to switch between two completely different β-peptide helices by relatively modest alteration of residue structure calls attention to a significant difference between α-amino acids and β-amino acids as building blocks: the chemist can exert much greater control over the intrinsic secondary structural propensity of β-amino acid residues than is possible with α-amino acid residues. This point is further illustrated by examples discussed below.



The prediction that oligomers of ACPC should form the 12-helix was born out in experimental studies,[77,106,149] in which relatively short oligomers were shown to adopt the 12-helix conformation, both in organic solution and in the solid state. In organic solvents, the conformation is so stable that it is observed in peptides containing as few as six ACPC residues. However, β-peptides consisting of this amino acid were not soluble in water. To address this limitation, the pyrrolidinyl amino acid *trans*-3-amino-pyrrolidine-4-carboxylic acid (APC) was prepared and incorporated into β-peptides along with ACPC residues (peptides **6**−**8**).[85] CD and NMR studies indicate that oligomers with as few as four residues showed substantial populations of the 12-helix in water and that the helical content increased with chain length.[85] Very efficient synthetic routes to either enantiomer of APC[150] or ACPC[151] have recently been developed, which should facilitate access to this class of β-peptides. In addition, side chains can be introduced at specific sites along a 12-helix by using sulfonylated APC (S-APC) residues.[152] Winkler et al. recently reported that β-peptides constructed from an ethanoanthracene-based monomer also adopt a single turn of 12-helix in organic solvent.[153]

Theoretical calculations[84] indicated that the $\pi-\pi^*$ contribution to the CD spectrum of the 12-helix should be similar in shape to that of the 14-helix but that the sign should be reversed for a given helical handedness and the splitting between the parallel and perpendicular bands should be greater. The experimental spectra observed for a hexamer that forms a left-handed 12-helix is consistent with this analysis, showing a maximum near 205 nm and a minimum near 190 nm. Additionally, a negative band is observed near 220 nm, which is probably associated with the $n-\pi^*$ transition. The presence of a maximum at 200−205 nm together with a minimum near 220 nm has not been observed in other secondary structures of β-peptides and may be diagnostic of the 12-helix.

C. 10/12-Helix

β-Peptides with alternating β^2- and β^3-monosubstituted residues can adopt the 10/12-helix conformation (Figures 1 and 3).[39,65] The characteristic feature

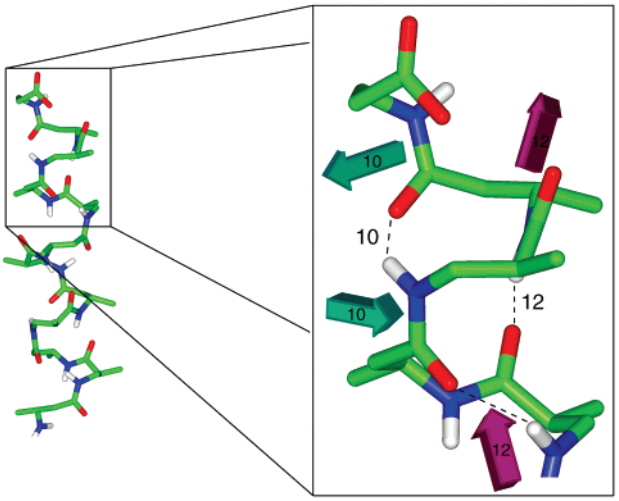


Figure 4. Structure of the 10/12-helix with zoom-in view of the two types of amide bonds. The hydrogens are omitted for clarity, except for the amide hydrogens (white). Carbon atoms are shown in green, nitrogen in blue, and oxygen in red. Vectors representing the 10-atom ring amides and the 12-atom ring amides are shown in cyan and magenta, respectively.

of this helix is an intertwined network of 10- and 12-membered hydrogen-bonded rings. This secondary structure is reminiscent of repeating nested turns, observed in designed peptides[154,155] and proteins.[156,157]

The 10/12-helix has been studied in organic solvents (pyridine and methanol) by CD and NMR. The circular dichroism spectrum of the right-handed 10/12-helical conformation shows an intense single peak near 205 nm with a mean residue ellipticity up to 60 000 deg cm^2 dmol^{-1}. In this helix (Figure 1C), amides surrounded by methylenes hydrogen bond to one another (*i, i+2*), forming the 10-membered rings, while the 12-atom rings are formed between amides surrounded by side chains (*i+1, i+3*). In contrast to the uniform alignment of amide bonds with the helical axis for the 14- and 12-helices, there are two types of amide bond orientations in the 10/12-helix (Figures 1, 3, and 4). The 10-atom ring amides are approximately perpendicular to the helical axis, while the 12-atom ring amides are nearly aligned with the helical axis (Figure 4). This results in a smaller overall helix dipole compared to the other helical conformations.

It has been speculated that the 10/12-helix is strongly encouraged when residues with interacting side chains are placed three residues apart (one 12-helix turn).[39,65] Thus, molecular mechanics calculations in solution were performed to understand the formation of the 10/12-helix.[69] Surprisingly, when considering only the backbone (oligo-β-alanine), the 10/12-helix was predicted to be intrinsically more stable than the 14-helix. Furthermore, when torsional and steric effects of methyl side chains were considered, the experimentally observed conformations were predicted for the various substitution patterns (Figure 5, Tables 3 and 4[69]). Interestingly, introduction of the methyl side chains resulted in the destabilization of the unfavored conformations, instead of the initially proposed stabilization of the favored conformation through side chain interactions.

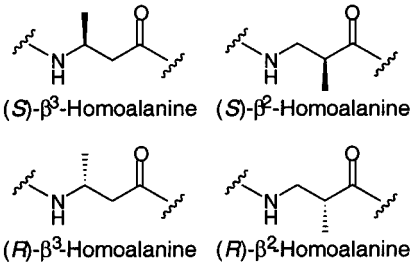


Figure 5. Four possible isomers of homoalanine (hAla) with different substitution position and configuration.

Table 3. Possible Substitution Patterns for hAla-hAla Repeats[a]

	(*S*)-β^2	(*R*)-β^2	(*S*)-β^3	(*R*)-β^3
(*S*)-β^2	**(*S*)-β^2/(*S*)-β^2**	(*R*)-β^2/(*S*)−β^2	(*S*)-β^3/(*S*)−β^2	(*R*)-β^3/(*S*)−β^2
(*R*)-β^2	**(*S*)-β^2/(*R*)-β^2**	(*R*)-β^2/(*R*)−β^2	(*S*)-β^3/(*R*)−β^2	(*R*)-β^3/(*R*)−β^2
(*S*)-β^3	**(*S*)-β^2/(*S*)-β^3**	(*R*)-β^2/(*S*)−β^3	**(*S*)-β^3/(*S*)-β^3**	(*R*)-β^3/(*S*)−β^3
(*R*)-β^3	**(*S*)-β^2/(*R*)-β^3**	(*R*)-β^2/(*R*)−β^3	**(*S*)-β^3/(*R*)-β^3**	(*R*)-β^3/(*R*)−β^3

[a] The bold combinations are the unique infinite repeats. The other repeats can be produced from the unique ones by sequence reversal or mirror operation.

Table 4. Structural Prediction for Unique hAla-hAla Repeats[69]

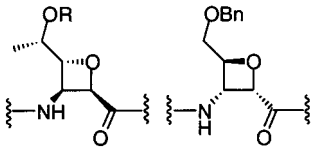
dipeptide repeat	predicted helical conformation
(*S*)-β^2/(*S*)-β^2	10/12-helix, 14-helix
(*S*)-β^2/(*R*)-β^2	10/12-helix
(*S*)-β^2/(*S*)-β^3	10/12-helix, 14-helix
(*S*)-β^2/(*R*)-β^3	10/12-helix
(*S*)-β^3/(*S*)-β^3	14-helix
(*S*)-β^3/(*R*)-β^3	10/12-helix

For the four possible monomethyl-substituted β-amino acids (Figure 5), there are only six unique combinations for an infinite dipeptide repeat (Table 3, the other combinations can be related by mirror operation or reverse of the repeat), and the theoretically predicted secondary structures are given in Table 4.[69] These predictions could enable the design of specific helices, but they remain to be fully tested experimentally. Furthermore, substitution patterns straddling two helical conformations may be useful in chemosensor development, as induced conformational changes may be exploited by detectable coupled events such as fluorescence resonance energy transfer. Indeed, the dramatic solvent-dependent change in the CD spectrum of a β-peptide has been suggested to arise from an environmentally induced switch between 10/12-helix (in water) and 14-helix (in methanol).[158] A comparable change in CD arising from end-group deprotection has been similarly rationalized.[39]

D. 10-Helix

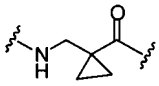
Fleet et al. recently prepared β-peptides from monomers with a four-membered ring constraint; these β-peptides display an unprecedented 10-helix secondary structure (Figure 1C).[159] The constitutent β-amino acids contain an oxetane ring (four-membered ring ether) and are derived synthetically from monosaccharides (see structures below). The amino and carboxyl substituents are cis on the four-membered ring, in contrast to the trans relationship for cyclohexane-, cyclopentane-, and pyrrolidine-

constrained residues discussed above. 10-Helical folding in nonpolar solvents (chloroform or benzene) was established by two-dimensional NMR analysis.



E. 8-Helix

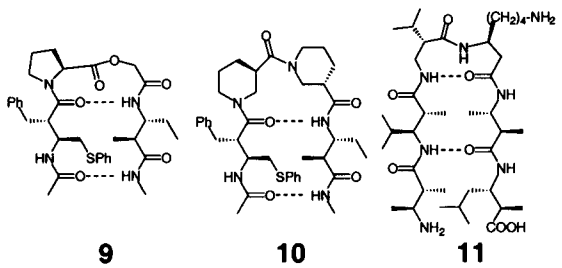
Crystal structures of short oligomers of the achiral monomer 1-(aminomethyl)cyclopropanecarboxylic acid reveal a propensity for this β-amino acid residue to form eight-membered ring hydrogen bonds.[160] These observations led Abele et al. to suggest that longer oligomers of this type may adopt a regular 8-helix, which would have approximately two residues per turn. A related structure has been proposed for oligomers of α-aminoxy acids.[36] α-Aminoxy acids are structurally related to β-amino acids; the β-carbon of the latter is replaced by an oxygen atom in the former.



IV. β-Sheetlike Conformations

There are in principle two types of sheet secondary structure available to β-peptides, one in which each residue has an anti C^2-C^3 torsion angle and another in which each residue has a gauche C^2-C^3 torsion angle.[67] The "anti" type of β-peptide sheet is distinctive since all backbone carbonyls are oriented in approximately the same direction, which would endow the resulting sheet with a net dipole. In contrast, β-sheets formed by α-peptides have little or no net dipole because the backbone carbonyls alternate in direction along each strand. β-Peptide sheets formed by residues with gauche C^2-C^3 torsion angles would lack a net dipole for the same reason.

Significant progress has also been made toward the goal of preparing β-peptides with sheetlike conformations. In early work poly-β-Ala was shown to crystallize as an extended sheetlike structure[49,50] but to be disordered in solution.[161] Sheet secondary structure has also been deduced for other poly-β-amino acids,[51,52] although other studies of similar polymers have led to the conclusion that helical conformations are preferred.[44−48]



9 **10** **11**

Designed hybrid molecule **9** has been shown in organic solution and in the solid state to adopt a hairpin-like conformation in which the two β-amino acid residues at either end engage in antiparallel sheet-type hydrogen-bonding interactions.[67] Molecule **9** contains a central D-Pro-glycolate sequence which promotes a β-turn-like conformation and initiates formation of an antiparallel sheet. The syn configuration of the substituents at C^2 and C^3 of the β-amino acid residues in **9** favors anti C^2-C^3 torsion angles because the alkyl substituents at these positions can adopt an energetically favorable anti-orientation only when the $N-C^3-C^2-C$ torsion angle is 180°. Replacement of the disubstituted β-amino acid residues of **9** with β-alanine led to formation of a nonpolar sheet in which both residues have gauche C^2-C^3 torsion angles, and replacement with β^3-residues led to equilibration between the two types of β-peptide sheet. These results suggest that disubstituted β-amino acid residues with the syn configuration have the highest sheet-forming propensity.

Further studies of β-peptide sheet secondary structure led to replacement of the -D-Pro-glycolate- turn-forming sequence in **9** with a heterochiral dipeptide composed of the Pro analogue nipecotic acid (Nip), as in **10**.[66] This tetrapeptide contains exclusively β-amino acid residues, with the central two residues constituting a β-peptide reverse turn. Homochiral dinipecotic acid segments (i.e., both nipecotic acid residues with the same absolute configuration) prevented sheet interactions between the terminal residues.

Seebach et al. used a similar strategy to stabilize the formation of β-peptide hairpins in organic solvent (peptide **11**).[86] They prepared a hexapeptide with the first two and last two residues being *syn*-C^2,C^3-disubstituted β-amino acids. Significantly, Seebach et al. found that a dipeptide sequence containing a C^2- followed by a C^3-substituted β-amino acid stabilized a reverse turn that is different from the reverse turn formed by the heterochiral dinipecotic acid segment (10-membered ring hydrogen bond in the former vs 12-membered ring hydrogen bond in the latter). The availability of two distinct types of reverse turn among β-peptides highlights the greater conformational diversity in this foldamer family relative to α-peptides in which only a single type of reverse turn (β-turn) is commonly observed. The extent of hairpin formation in peptide **11** has been examined by molecular dynamics calculations using the X-PLOR together with NMR-derived distance constraints.[86] Also, two 100 ns unrestrained molecular dynamics of the peptide in methanol at 298 and 340 K were conducted using GROMOS.[75] The simulations with experimental restraints indicated that the turn was formed in the majority of the structures and that the N- and C-terminal ends of the structure adopted a primarily extended antiparallel orientation, although they were not in hydrogen-bonding distance. The unrestrained simulation at 340 K gave the best agreement with experiment and showed that the turn was present only 30% of the time. Interstrand interactions between the bulky side chains

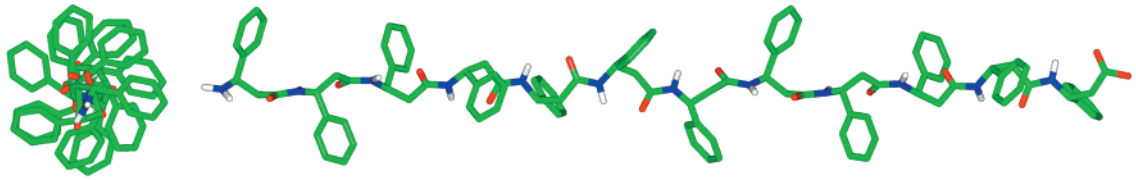


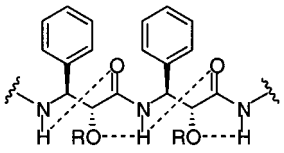
Figure 6. Top view (left) and side view (right) of the twisted strand conformation. The *tert*-butyldimethylsilyl-protected hydroxymethyl side chains and hydrogens are not shown for clarity, except for the amide hydrogens (white). The carbon atoms are shown in green, nitrogen in blue, and oxygen in red.

were suggested to account for the relatively low population of the desired hairpin structure.

V. Other Secondary Structures

A. Twisted Strands

The homooligomer of *tert*-butyl-dimethylsilyl-phenylisoserine adopts a twisted strand conformation in chloroform as revealed by NMR (Figure 6).[162] In contrast to the interstrand hydrogen bonds for hairpin structures discussed above, this twisted strand conformation exhibits bifurcated hydrogen bonds in an intrastrand fashion involving backbone and side chain functionalities. Furthermore, the residues adopt a gauche conformation for this twisted strand, resulting in a 13-residue repeating structure (Figure 6). The structure appears to be held together by electrostatic, van der Waals interactions, and bifurcated hydrogen bonds.



In aqueous solution, β^3-hAla-based peptide nucleic acids exhibit unique strand pairing behavior, which has been explained by strand orientations and base pairing interactions within the context of an extended backbone conformation.[17,163] In this case, the structure is most likely dictated by the hydrogen bonding and aromatic π-stacking of the nucleobase-containing side chain. Further investigation with NMR or crystallography will be necessary to reveal the structural details of these β^3-hAla-based peptide nucleic acids.

B. Non-Hydrogen-Bonded Structures

Oligo-PCA, oligo-Nip, and oligo-β^3-homoproline β-peptides seem to form yet another secondary structure or set of secondary structures in methanol,[92,93] presumably analogous to the polyproline helices, since these β-amino acids are similar to proline in lacking hydrogen-bond donating ability. The CD spectrum of oligo-PCA exhibits a strong minimum near 214 nm, and oligo-Nip displays a weak maximum at 228 nm and strong minimum at 208.[92,93] The length dependence of these β-peptides has been investigated by CD in methanol;[93] at least four residues are needed to form the regular secondary structure. Detailed elucidation of these non-hydrogen-bonded structures will require methods of higher resolution such as NMR or crystallography.

VI. Biologically Active β-Peptides

The finding that β-peptides are able to adopt stable helical, turn, and sheet conformations has provided a useful starting point for the design of functional mimics of natural peptides and proteins. β-Peptides are stable to proteolytic degradation in vitro and in vivo,[104,164,165] an important advantage over natural peptides and proteins. To date, natural peptides with relatively simple secondary structures have been the target of these investigations. However, as the field progresses, it should also be possible to design β-peptides whose activities depend on the formation of well-defined tertiary structures as well.

A. Inhibitors of Fat and Cholesterol Absorption

Seebach and co-workers designed amphiphilic 14-helical β-peptides intended to mimic the amphiphilic α-helices of human apolipoproteins involved in lipid uptake and transport.[166] Apolipoproteins play an important role in the docking and uptake of lipoprotein particles in the small intestinal brush-border membrane, in a process mediated by the class B scavenger receptors.[167] Because amphiphilic α-helical peptides are able to inhibit this process, it was expected that appropriately designed β-peptides might also be efficient inhibitors. Significantly, a series of amphiphilic 14-helical β-peptides inhibited oleoyl ester uptake by brush-border vesicles, and β-peptides that could not adopt amphiphilic helix conformations were inactive. Further, the amphiphilic helical β-peptide inhibited the facilitated transport of cholesterol through monolayers of CaCo-2 cells (a model for the intestinal epithelial layer). The β-peptides had relatively high IC_{50} values on the order of 0.5−1.0 mM, but a number of controls suggested that they were inhibitors of a specific receptor-mediated process. The active β-peptides are approximately one-half the length of active α-helical peptides, and these β-peptides are resistant to proteolytic degradation. Thus, these β-peptides should be considered as promising first-generation models with potential for significant enhancements in potency.

B. Antibacterial β-Peptides

Antimicrobial peptides are an important component of the innate immune systems and toxins of a large number of vertebrate and invertebrate species.[168] These peptides kill bacteria by interacting with and disrupting the integrity of the cellular

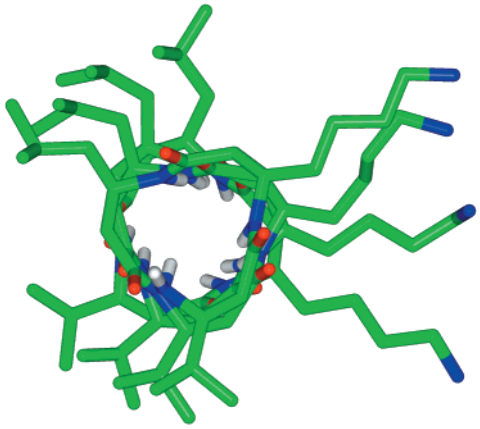


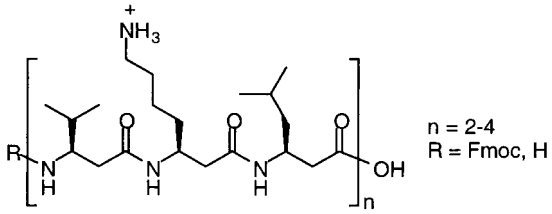
Figure 7. Molecular model of an amphiphilic β-peptide; the hydrogens are omitted for clarity except for the amide hydrogens (white). This view shows the segregation of hydrophobic and positively charged residues on opposite sides of the helix. Carbon atoms are shown in green, nitrogen in blue, and oxygen in red.

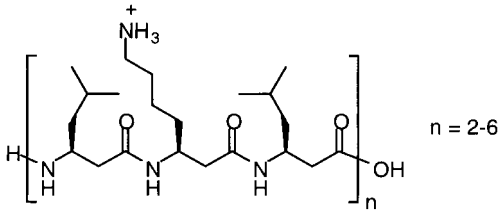
membranes of their targets.[169,170] It has long been hypothesized that the overall physicochemical properties of the peptides—and not their precise amino acid sequence, secondary structure, or chirality—are essential for their biological properties.[171] For example, a large number of cytotoxic and antimicrobial peptides adopt a highly positively charged, amphiphilic α-helix in which hydrophobic and positively charged side chains segregate onto opposite faces of the cylindrical secondary structure.[169−171] These amphiphilic helices disrupt membranes by inserting their hydrophobic side chains into the outer leaflet of the membrane, leading to a surface pressure and chemical potential imbalance between the two leaflets of the bilayer.[172] After the initial binding, the peptides can either insert to form ion-conducting channels or lead to more generalized disruption of the membrane.[169,170] In either case the result is the same: a breakdown of the transmembrane potential, leakage of portions or all of the cellular content, and ultimately cell death.

Previously, antimicrobial peptides were designed by idealizing the amphiphilic α-helical arrangement of side chains observed in the natural structures, leading to a large number of potent and selective antimicrobial compounds.[169−171,173−175] The availability of β-peptides provided another avenue to test and further elucidate the features required for the construction of bacteriacidal agents. Two classes of antimicrobial β-peptides have been prepared that form either 14-helical[111,176] or 12-helical[177] conformations.

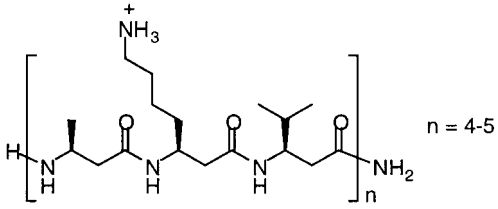
The 14-helix has an approximate three-residue geometric repeat. Thus, if polar and apolar side chains are arranged with precise three-residue periodicity in the sequence of a β-peptide, they will segregate to opposite sides of the helix (Figure 7). To test this hypothesis, two series of repeating tripeptides were prepared with β^3-hLeu and/or β^3-hVal chosen as a hydrophobic residue and β^3-hLys as a polar, positively charged amino acid.[111] Because helix formation was expected to be length-dependent, the number of tripeptide repeats was modulated from 2 to 6. The biological activities of the peptides were measured using *E. coli* as a model for bacteria and human erythrocytes as a model for mammalian cells. The compounds were shown to have highly potent cell-lytic activity, with the longest peptides showing IC_{50} values in the nanomolar range. As is the case for α-helical antimicrobial peptides, the β-peptides appeared to adopt largely unfolded conformations in aqueous solution but well-defined secondary structures upon binding to phospholipid bilayers and micelles. For these β-peptides the minimal length for the formation of a 14-helix was 9−12 residues, which also coincided with the minimal length required for biological activity. Thus, the helical conformation appeared to be necessary to their biological activities.

First Series

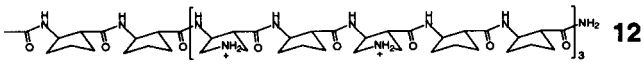




Second Series



Although these peptides were highly potent antimicrobial agents, they generally showed poor discrimination between bacteria versus red cells. Natural antimicrobial peptides are believed to target bacteria because their membranes generally bear more negatively charged lipids than mammalian cells. Often, selective binding to bacterial membranes requires a careful balance of not only the charge, but also the helix-forming potential and hydrophobicity.[169,170,173,178−180] In particular, analogues of antimicrobial peptides that are too hydrophobic tend to have poor selectivity for bacteria versus mammalian cells.[170,173] Therefore, a second series of peptides was prepared in which the hydrophobic β^3-hLeu or β^3-hVal was replaced with a less hydrophobic β^3-hAla.[176] The resulting peptides showed potencies and selectivities comparable to those of natural antimicrobial peptides such as magainin. They also showed a strong tendency to bind to and disrupt the integrity of acidic but not neutral phospholipid membranes.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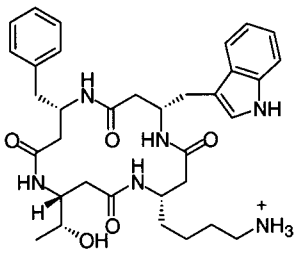
It has also been possible to design antimicrobial β-peptides that adopt 12-helical rather than 14-helical structures.[177] Compound **12** contains positively charged APC and hydrophobic ACPC β-residues arranged in sequence to segregate onto opposite faces of a 12-helix. This β-peptide was highly potent and highly specific toward bacteria, showing excellent activity against four species (including both Gram-positive and Gram-negative organisms**)** and minimal lytic activity against human erythrocytes. It is interesting to note that compound **12** is much more rigid than β-peptides composed of β^3-monosubstituted amino acids. Nevertheless, it has been possible to obtain highly selective antimicrobial compounds from both structural classes. Thus, there appears to be no a priori requirement for flexibility or rigidity so long as the hydrophobicity−charge balance and length are appropriately optimized within a given class of compounds.

C. Cyclic β-Peptides

Several groups have described a series of cyclic β-peptides and mixed α- and β-peptides that self-assemble to form tubular architectures. For example, a tetrapeptide that contains alternating α- and β-amino acids, cyclo[Ser(O^{t}Bu)-β-Ala-Gly-β-Asp(OMe)], crystallizes into a tube-like arrangement of monomers, featuring intermolecularly hydrogen-bonded stacks of rings.[53] Seebach and co-workers also studied a series of methyl-substituted cyclic tetrapeptides which appear to form tubular stacks of hydrogen-bonded rings.[60] Building on these observations, Ghadiri et al. showed that cyclic-β-peptides form tubular ion-conducting channels in phospholipid bilayers.[61]

Seebach and co-workers designed cyclic β-peptide **13** to mimic of the peptide hormone somatostatin. This cyclic oligomer bound to the various somatostatin receptor subtypes with affinities ranging from 3 to 200 μM, as compared to from 0.1 to 1.2 nM for somatostatin itself.[181] NMR structural investigations[182] showed a significant, although not perfect, overlap between cyclic β-peptide **13** and highly active cyclic peptide mimics of somatostatin. Thus, the potency of the β-peptide might be improved through repeated rounds of design, synthesis, and testing. This group has also designed a series of mimics of the enterobactins, which play important roles in the uptake of iron in bacteria.[183]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VII. Conclusions

β-Peptides represent a very small subset of the possible sequence-specific oligomers that chemists might consider for the design of biomimetic structures. Although they have been intensively studied for a relatively short period of time, a surprisingly large number of structures and functions have been designed or discovered within this class of compounds. The application of combinatorial methods to the synthesis of β-peptides should result in the discovery of ligands for a variety of pharmaceutically relevant targets, as has been the case for peptoids.[20,184−187] Clearly, the design of β-peptides that adopt well-defined tertiary structures represents an additional challenge with fundamental implications for understanding molecular assembly and protein folding as well as practical implications for the design of pharmaceuticals, materials, and molecular devices.

VIII. Acknowledgements

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IX. Note Added in Proof

Cheng and Deming recently reported transition-metal catalysts for living polymerization of β-lactams to create β-peptide block co-polymers (Cheng, J.; Deming, T. J. *J. Am. Chem. Soc.* **2001**, *123*, 9457−9458. Karle et al. showed that β^3-amino acids can be accommodated, with a local anti conformation, into an α-peptide β-hairpin (Karle, I. L.; Gopi, H. N.; Balaram, P. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 3716). Gademann et al. described a linear tetra-β-peptide that shows selective affinity for human somatostatin receptor 4 (Gademann, K.; Kimmerlin, T.; Hoyer, D.; Seebach, D. *J. Med. Chem.* **2001**, *44*, 2460).

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