ACCOUNTS
of chemical research

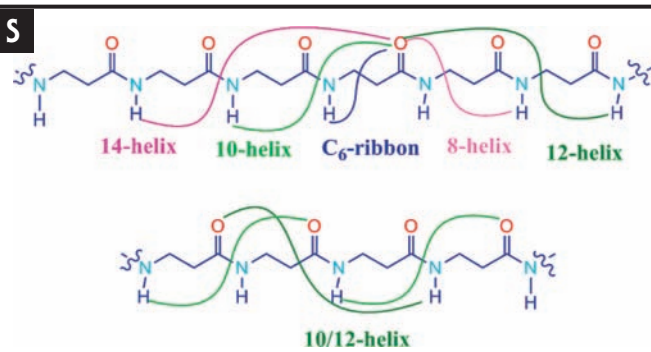
Theoretical Analysis of Secondary Structures of β-Peptides

YUN-DONG WU,* WEI HAN, DE-PING WANG, YI GAO, AND YI-LEI ZHAO

Department of Chemistry, The Hong Kong University of Science & Technology, Clear Water Bay, Kowloon, Hong Kong, China

RECEIVED ON MARCH 4, 2008

CONSPECTUS



Unlike α-amino acids, peptides formed from β-amino acids (β-peptides) display stability toward enzymatic degradation and may form turns and helices with as few as four residues. Because both the C_α and C_β of the β-amino acid may bear substituents, a large number of β-amino acids can be synthesized. β-Peptides form various well-defined secondary structures, including 14-helix, 12-helix, 10/12-helix, 10-helix, 8-helix, turn structures, sheets, and hairpins. For all of these reasons, β-amino acids have been increasingly used as building blocks for molecular design and pharmaceutical applications.

To explain the conformational features of β-peptides, several quantum mechanics and molecular dynamics studies that rationalize the observed conformational features have been reported. However, a systematic account that unifies various factors critical to the conformational features is still lacking. In this Account, we present a detailed analysis of the conformational features of various β-peptides. We start by studying the basic local conformational features of β-peptides using di- and tripeptide models. Then, various secondary structures of unsubstituted β-peptides with differing numbers of residues are investigated using a repeating unit approach to derive the intrinsic backbone conformational features.

We find that the 10/12-helix is intrinsically most stable for the β-peptide backbone. The 14-helix, 12-helix, and 10-helix structures have similar stabilities for β-peptide backbones of four to six residues. The substituent effects on the stabilities of β-peptide secondary structures are then analyzed. Combined with the substituent effect and the intrinsic backbone preferences, all experimental observations of secondary structure formation can be understood. For example, the 10/12-helix is favored for like-β^2/β^3-peptides, unlike-β^3/β^3-peptides, and β^3/β-hGly-peptides because these substitution patterns do not cause steric problems for the 10/12-helix. β^3-Peptides, β^2-peptides, and $\beta^{2,3}$-peptides favor the 14-helix because the substituents in these peptides benefit the 14-helix the most but significantly destabilize the 10/12-helix. Because the 10/12-helix is intrinsically favored and has two favorable positions in each residue for substituents, many more hybrid β-peptides are predicted to exist in this secondary structure, which suggests the need for further experiments. These results are valuable for determining the best use of these building blocks in the design of well-structured molecules with desirable chemical functions.

Introduction

The β-Peptide, formed by β-amino acids (β-AAs), has been a subject of intensive study in the past decade.[1−3] Several major findings have been made: (1) β-Peptides can form various well-defined secondary structures.[4−6] Unlike α-peptides, β-peptides as

Published on the Web 10/02/2008 www.pubs.acs.org/acr
10.1021/ar800070b CCC: $40.75

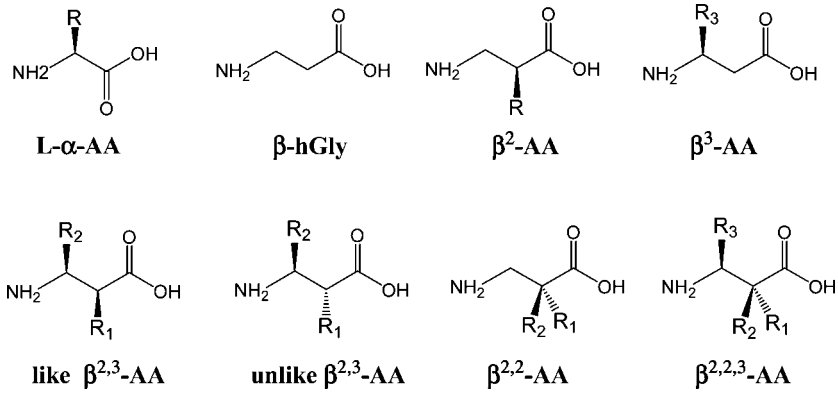


FIGURE 1. Schematics of α-amino acids and β-amino acids.

short as four residues may form helical or turn structures in hydroxylic solvents, allowing structure-based molecular design. (2) In contrast to α-peptides, β-peptides normally display stability toward enzymatic degradation,[7] such as proteolytic[8] and metabolizing enzymes in microorganisms,[9] insects,[10] and mammals.[11] This makes β-amino acids useful building blocks in peptidomimetic drug design. (3) Significant progress has been made in using β-peptides to mimic biological functions of α-peptidic secondary structures. These include antibiotic,[12−14] anticancer,[15−18] and anti-HIV functions,[19,20] DNA[21,22] and RNA[23] binding, and cell penetration.[24]

Since a β-amino acid can have substituent(s) at both C_α (C_2) and C_β (C_3) positions, in principle, a β-amino acid has much richer possible derivatives than an α-amino acid. Indeed, many methods have been developed for the synthesis of β-AAs.[25−28] Given in Figure 1 are some β-AAs. The parent β-AA is often called β-hGly or β-Ala. β^2-AAs and β^3-AAs have a substituent at the C_α and C_β positions, respectively. When both C_α and C_β are alkyl-substituted, we can have like [(*R*,*R*) or (*S*,*S*) configuration] and unlike [(*R*,*S*) or (*S*,*R*)] $\beta^{2,3}$-AAs. Other types of di- and trisubstituted β-AAs are defined in a similar way. It is expected that the bank of β-peptide derivatives is very rich by combining different types of β-AAs to form amide bonds.

As shown in Figure 2, a β-peptide can form various different patterns of hydrogen bonds, which result in various secondary structures. The stereoviews of these secondary structures are shown in Figure 4a. A 14-helix is formed by contiguous 14-membered ring (14-mr) hydrogen bonds between the N−H of the *i*th residue and the C═O of (*i* + 2)th residue. In a similar way, a 12-helix is formed by contiguous 12-mr hydrogen bonds between the C═O of the *i*th residue and the N−H of (*i* + 3)th residue. A 10-helix has contiguous 10-mr hydrogen bonds. If contiguous 8-mr and 6-mr hydrogen bonds are formed, these structures are called 8-helix (or 2_8-ribbon) and C_6-ribbon, respectively. A special helical structure with alternate 10-mr hydrogen bonds and 12-mr hydrogen bonds is named 10/12-helix. Different from other helical structures, which have all the carbonyl groups oriented in the same direction, the 10/12-helix has adjacent C═O groups in alternate up and down orientations. Of course, a β-strand is also possible, which has all the carbonyl groups oriented in nearly the same plane, allowing intermolecular hydrogen bond formation to form sheet structures.

While the secondary structures of α-peptides are significantly affected by side chain properties, the secondary structures of β-peptides appear to be mainly determined by the substitution patterns. The groups of Gellman and Seebach discovered the 14-helix at about the same time.[29,30] While Gellman's group studied β-peptide formed by (*S*,*S*)-2-aminocyclohexane carboxylic acid (*trans*-2-ACHC),[30−33] a special class of $\beta^{2,3}$-peptide with a six-membered backbone ring, Seebach's group studied β^2- and β^3-peptides.[29,34−37] Later, Seebach et al. found that (*S*,*S*)-$\beta^{2,3}$-amino acids can also form 14-helix.[38] In the case of *trans*-2-ACHC, peptides as short as five to six residues can exist in the 14-helix. Shortly after the discovery of the 14-helix, Seebach's group reported the formation of the 10/12-helix by like-β^2/β^3-peptides with alternate β^2- and β^3-AAs in the same configuration,[39,40] (like- is dropped hereafter). Later, unlike-β^3/β^3-peptides[41] and β^3/β-hGly-peptides were also found to form the 10/12-helix.[41] Thus, the 10/12-helix appears to be formed by alternate β-AA units. The report by Gellman's group of the formation of 12-helix by $\beta^{2,3}$-peptides composed of *trans*-2-aminocyclopentanecarboxylic acid (ACPC) and *trans*-3-amino-pyrrolicine-4-carboxylic acid (APC) is very interesting because these β-AA units have five-membered ring backbones.[42−45] A 10-helix was reported by Fleet et al. for the β-peptide formed by monomers with a four-membered ring constraint.[46] The structural features of $\beta^{2,2}$-peptides were also studied. While the solution structure of $\beta^{2,2}$-peptides by dimethyl substitutions could not be determined with certainty,[47] the 8-helix was found

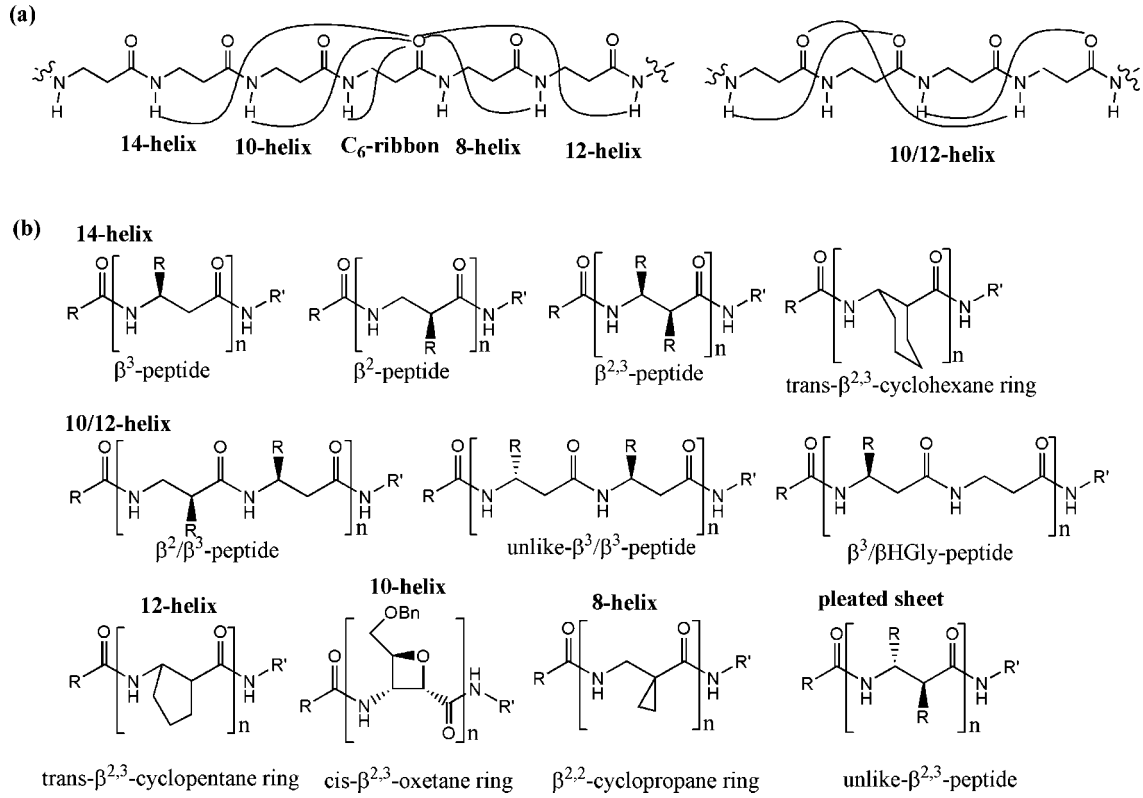


FIGURE 2. Summary of observed secondary structures of β-peptides.

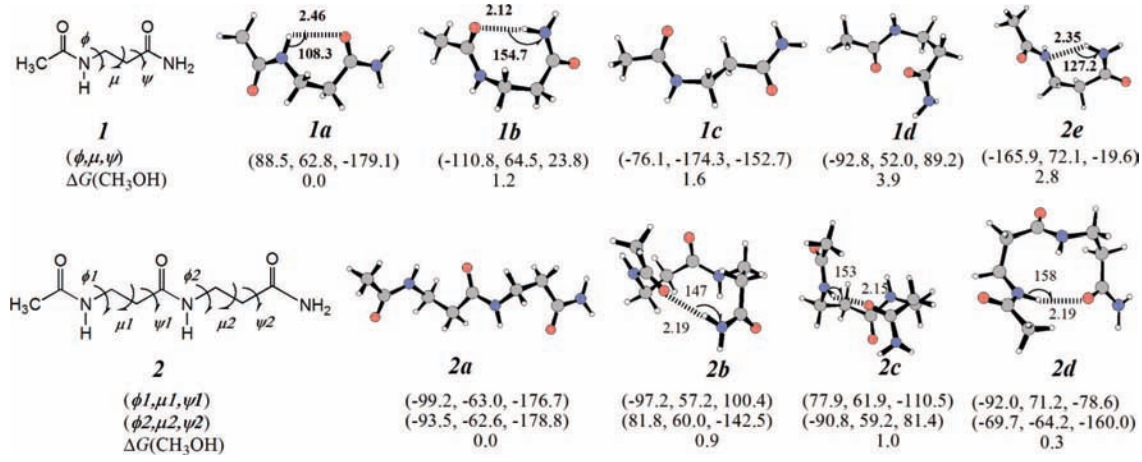


FIGURE 3. Conformational features of the parent β-dipeptide and β-tripeptide models. Relative free energies are in kcal/mol.

when the β-peptide has a cyclopropane ring at the C_α position.[48] An 8-helix structure was found for oxanornene β-peptide with constraint of $C_\alpha-C_\beta$ dihedral angle to about 120°[49] and β-peptide consisting of (2*R*,3*S*)-3-amino-2-hydroxy acid residues.[50] In addition, β-turns,[47,51] hairpin[52−56] and parallel-pleated sheet[57] structures were also found for β-peptides.

Many theoretical studies of β-peptides have been reported.[49,58−77] We[58−62] and Hoffmann's group[63−67] have carried out extensive quantum mechanics studies of short β-peptides both in the gas phase and in solution. Van Gunsteren and Seebach reported a series of molecular dynamics studies on the conformational distributions and dynamic features of β-peptides.[68−77] These studies in general reproduce the observed structural features well. In some cases, predictions were made that were later confirmed by experiments.[49,59,63] However, a systematic account of the conformational features of these peptides, especially systematic evaluation of the substituent effects on secondary structure formation is still lacking.[59,65] This paper summarizes the results from quantum mechanics studies and provides a systematic analysis of the conformational features of these peptides for a more detailed understanding of the observed

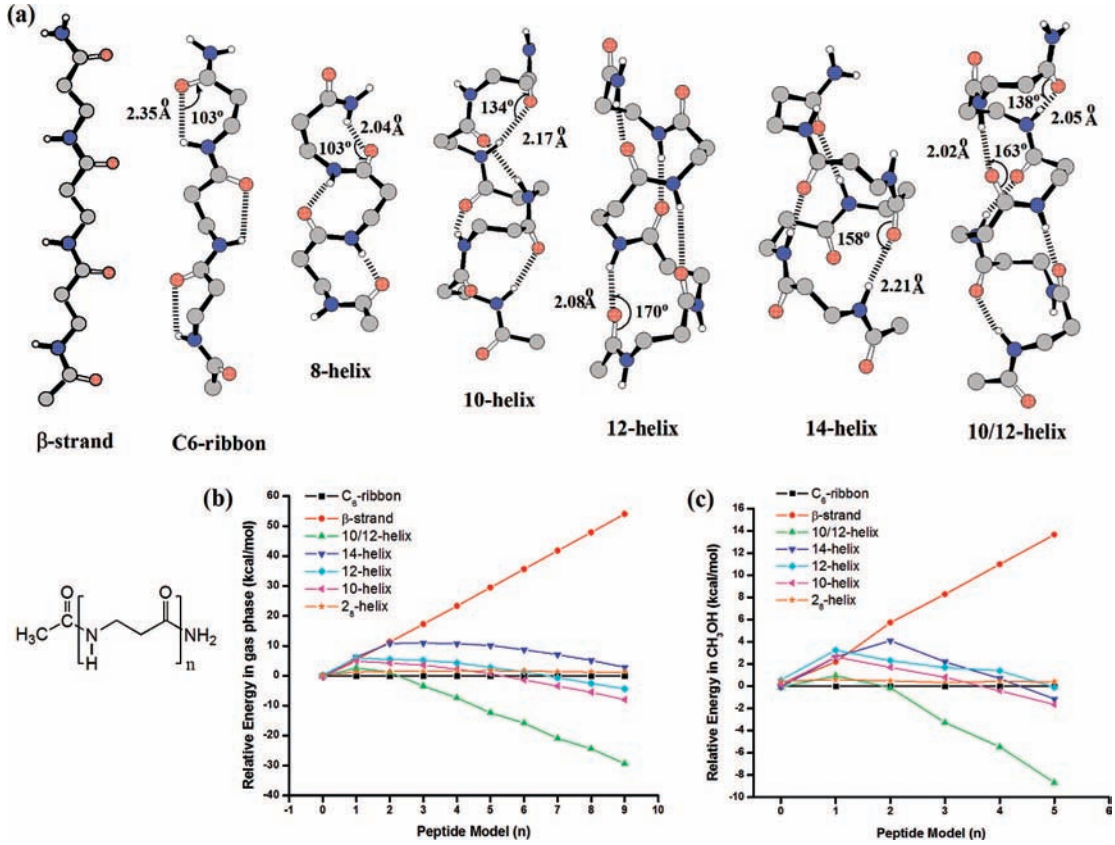


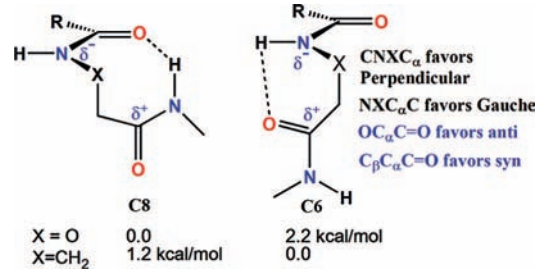
FIGURE 4. The stereoviews and energetics of various secondary structures of β-peptides

conformational features of these peptides. A summary on the molecular dynamics studies can be found in ref 5.

Conformational Features of Unsubstituted β-Dipeptide

A study of a dipeptide model **1** is useful to obtain the local conformational features of β-peptide. Several stable conformations of **1** are shown in Figure 3. Calculations indicate that the most stable conformation is a C6 structure (**1a**).[58] Based on a long (N)H···O distance of 2.46 Å and a small N−H···O angle of 108°, this structure has only a weak hydrogen bond. The second most stable conformation is **1b**, which has a strong 8-mr hydrogen bond. This structure is less stable than **1a** by about 1.2 kcal/mol in methanol. This conformational preference of unsubstituted β-dipeptide is very different from that of α-aminoxy dipeptide.[78] As shown in Scheme 1, α-aminoxy peptide can be considered as derived from β-peptide by replacing C_β (C_3) with O (X = O). This type of peptide has been found to show a characteristic tendency to form eight-membered ring hydrogen-bond local structure, leading to 8-helix (or 2_8-ribbon) structure for homologous peptides.[79] An α-aminoxy-dipeptide can also have C6 and C8 conformations, but its C8 structure is calculated to be more stable than the C6 structure by about 2.2 kcal/mol in methanol. The dramatic difference in the conformational features between β-peptide and α-aminoxy-peptide can be mainly attributed to the conformational preference of the O=C−C_α−X dihedral angle. For α-aminoxy-peptide (X = O), O=C−C_α−O strongly favors to be anti (about 180°) instead of syn (about 0°), because the syn conformation would have considerable electrostatic repulsion between the two oxygen atoms. Thus, the C6 structure, which has syn O=C−C_α−O, is destabilized. On the other hand, for β-peptides (X = CH_2), there is a preference for O=C−C_α−C_β to be syn, also because of electrostatic reasons. Therefore, the C6 conformation is favored over the C8 conformation.

SCHEME 1. Backbone Conformational Preferences of α-Aminoxy Peptide and β-Peptide



For the β-dipeptide, the conformations corresponding to those in 10/12-helix (**1d**) and 14-helix (**1e**) (Figure 3) are found to be local minima, although they are less stable than

TABLE 1. Calculated Geometrical Parameters (Experimental Data in Parentheses) of Secondary Structures of β-Peptides[a]

structure	residues/turn	rise (Å)	pitch (Å)	φ (deg)	μ (deg)	ψ (deg)
C_6-ribbon	1.7	4.0	6.8	99.2	62.9	175.8
β-strand		4.9		180.0	180.0	180.0
10/12-helix	2.7	2.1	5.7	−99.3/89.5	61.3/65.9	89.9/−110.6
14-helix	3.1 (3.0)	1.7 (1.6)	5.2 (5.0)	−141.6	59.9	−133.3
12-helix	2.7 (2.5)	2.2 (2.1)	5.9 (5.6)	−88.5	89.3	−111.4
10-helix	2.6	2.3	6.0	73.5	51.3	73.6
2_8-ribbon	2.2	3.0	6.7	−111.5	68.6	13.9

[a] See Figure 4 for structures.

the C6 conformation. It is noted that these structures, along with the C6 and C8 structures, all have a gauche N−C_β−C_α−Csp2 dihedral angle. We believe that this gauche conformation is stabilized by electrostatic interactions between the negatively charged N and partially positively charged Csp2, as shown in Scheme 1. Since such a gauche conformation is required for helical structures, we propose that this is one of the reasons why β-peptides tend to form various helical structures.

A conformational study of unsubstituted β-tripeptide model **2** (Figure 3) reveals further interesting conformational features of β-peptides. While the conformation with two consecutive C6 units (**2a**) is still most stable, and conformations with two consecutive C8 units are unstable (not shown),[59] three structures with 10-mr and 12-mr hydrogen bonds (**2b**−**d**) are found to be reasonably stable, as shown in Figure 3.

Structures **2b** and **2c** have 12-mr and 10-mr hydrogen bonds, respectively. They have similar stabilities in CH_3OH solution, both being about 1 kcal/mol less stable than **2a**. Both of them have alternate up and down carbonyl groups. The six dihedral angles from ϕ_1 to ψ_2 are almost symmetrical, especially in **2c** (77.9°, 61.9°, −110.5°, −90.8°, 59.2°, and 81.4°). Most importantly, ϕ_1, μ_1, and ψ_1 of **2b** are almost the same as ϕ_2, μ_2 and ψ_2 of **2c**, and vice versa. These observations indicate that if an additional β-peptide residue extends at either end of structure **2b** or **2c**, a new 10-mr or 12-mr stable hydrogen bond will form, resulting in a repeating unit of the 10/12-helix. The results indicate that the 10/12-helix may be intrinsically favorable for the β-peptide backbone.

Structure **2d** is also in a 10-mr strongly hydrogen-bonded structure. It is a perfect turn structure. We predict that in CH_3OH this structure is only about 0.3 kcal/mol less stable than **2a**.[59] This suggests that a β-hGly-β-hGly unit might be a potential β-turn promoter in designing a hairpin structure. Indeed, this unit is found in many cyclic peptides and has been suggested to form a turn structure. Both **2c** and **2d** have been found to be turn structures of β-peptides.[51−56]

10/12-Helix Is the Intrinsically Most Favorable Secondary Structure of Unsubstituted β-Peptide

To have a better understanding of the secondary structure formation of β-peptides, we followed the strategy of studying the intrinsic backbone preference first, followed by further consideration of the substituent effects of various substitution patterns on the stabilities of secondary structures. Therefore, by using a simple repeating unit method, we theoretically studied the preferences for C6-ribbon, β-strand, 8-helix, 10-helix, 12-helix, 14-helix, and 10/12-helix structures of a series of poly-β-hGly models, Ac-(β-hGly)$_n$-NH_2, with *n* up to nine residues.[60]

Geometry. Figure 4a shows fragments of the seven secondary structures. Some geometrical parameters are given in Table 1. The C6-ribbon has a long O···H(N) distance of 2.35 Å but a very small O···H−N angle of 103°. Therefore, there is no strong hydrogen bonding. Each residue rotates by about 240°, and about 1.5 residues finish a turn. The 8-helix is very similar to the C6-ribbon, but the larger ring is relatively more flexible and thus has stronger hydrogen bonds. The β-strand has all the carbonyl groups on one side. Each residue extends about 5 Å. However, the carbonyl groups form a convex structure instead of being perfectly parallel. This is because the O=C−C_α and O=C−N angles are about 122.5°, while the C_α−C−N angles are only about 115°. The 10/12-helix has alternate 10-mr and 12-mr hydrogen-bonded structures and features alternating up and down dipoles. Therefore, the 10/12-helices have small dipole moments. The 12-mr has a larger O···H−N angle (163°) than the 10-mr (138°) has. We expect that the 12-mr possesses somewhat larger stability than the 10-mr does. The 10-mr in the 10-helix structure is different from the 10-mr in the 10/12-helix structure. The three dihedral angles (φ, μ, ψ) all have positive values (74°, 51°, 74°). Compared with the 14-helix structure, the 12-helix structure has shorter O···H(N) distances and larger O···H−N angles for the hydrogen bonds. As shown in Table 1, the calculated values of the φ, μ, and ψ dihedral angles for these

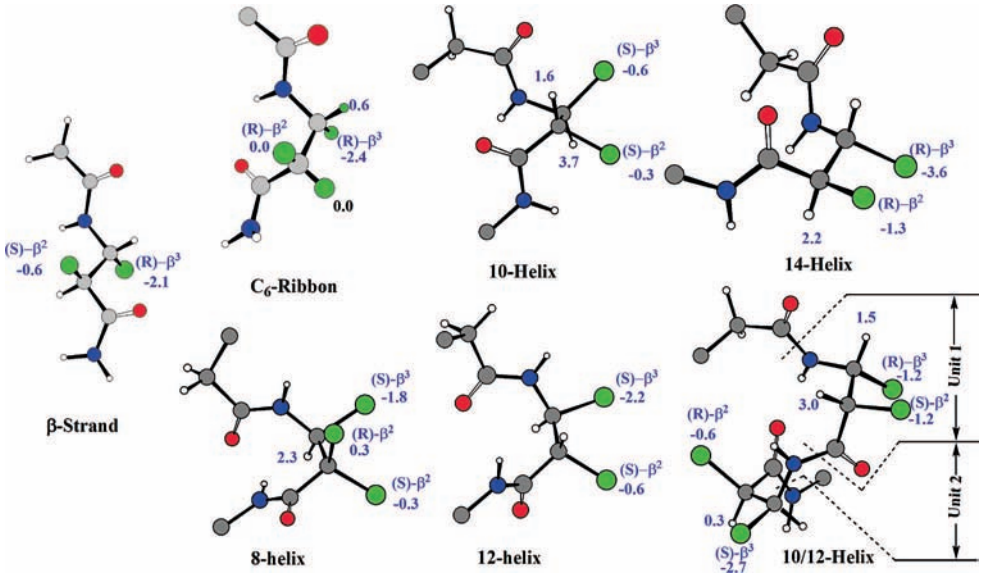


FIGURE 5. Estimated substituent effects on the stabilities of various secondary structures of β-peptides. All structures are in right-handed rotation. The values are relative energies of methyl substituents with respect to the methyl substituent at the β^2 of C6-ribbon.

structures are in close agreement with reported X-ray crystal structures.[30,42]

Relative Stabilities in the Gas Phase. Figure 4b gives the plots of the calculated relative energies of these secondary structures with respect to the C6-ribbon structure in the gas phase.[60] Several features are apparent. (1) The C6-ribbon is the most stable when $n = 1-2$. (2) The energy of the 8-helix is almost parallel and very close to the energy of the C6-ribbon. (3) The relative energy of the β-strand linearly increases with respect to the C6-ribbon. Each residue of the β-strand is about 6 kcal/mol less stable than that of C6-ribbon. This large distabilization is apparently due to repulsions between neighboring dipoles. (4) The 10-helix and 12-helix have similar stabilities, and they are stabilized with respect to C6 when n is increased. (5) The 14-helix is the least stable helical structure in the gas phase, and it is about 7−9 kcal/mol less stable than the 10-helix and 12-helix. As will be shown later, this situation changes in methanol solution. (6) For peptides with more than two residues, the 10/12-helix is the most stable. The preference for this helical structure over the other secondary structures increases significantly when the peptide becomes longer. This clearly indicates a large intrinsic preference for a β-peptide to adopt the 10/12-helical structure in the gas phase.

Relative Stabilities in Methanol Solution. SCIPCM model calculations of the effects of methanol solvent on the stabilities of the secondary structures indicate that the β-strand and 14-helix benefit significantly from the solvent effect. The 10-helix and 12-helix are stabilized to a smaller extent. The C6-ribbon and 8-helix are even less stabilized because of their reduced dipole moments compared with the 14-helix. The 10/12-helix, which has the smallest dipole moment, is least stabilized by the polar solvent.

The calculated relative energies of the seven secondary structures in methanol solution are plotted in Figure 4c. The 10/12-helix is still the most stable structure for peptides with more than two residues. The β-strand is still the least stable, but its destabilization is significantly reduced. The most interesting feature is the relative stability of the 12-helix and 14-helix. In the gas phase, the 12-helix is more stable than the 14-helix by about 6−8 kcal/mol, while in methanol solution, the 14-helix becomes more stable for peptide models with more than four residues.

Substituent Effects on the Stabilities of Various Secondary Structures of β-Peptides

The substituent effects on the stabilities of these secondary structures were studied by adding methyl groups at different positions of these structures. Shown in Figure 5 are the repeating units of the seven secondary structures of β-peptide. These structures are arranged in right-handed rotation for consistency. For each structure, the favored substitution positions are indicated by large circles. The numbers given to different positions are the estimated relative stabilities for methyl substitutions at those positions with respect to the methyl substitution at the C_α of the C6-ribbon. The positions without a number indicate that methyl substitutions cause significant destabilization and can be ruled out.

The results indicate that for a β^2-amino acid with a methyl substituent at C_α, the most favored positions are (*R*)-β^2 of the

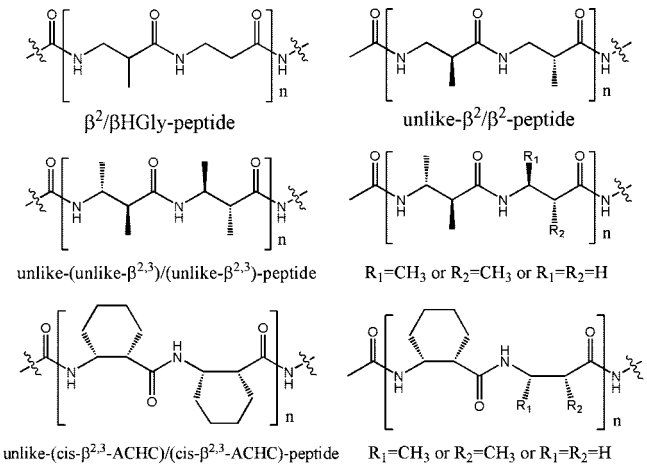


FIGURE 6. Predictions of hybrid β-peptides that may adopt 10/12-helix secondary structure based on the results in Figure 5.

14-helix (−1.3 kcal/mol) and (*S*)-β^2 of unit 2 of the 10/12-helix (−1.2 kcal/mol). For a β^3-amino acid with a methyl substituent at C_β, the most favorable positions are (*R*)-β^3 of the 14-helix (−3.6 kcal/mol) and (*S*)-β^3 of unit 1 of the 10/12-helix (−2.7 kcal/mol). Of course, these results can also be applied to left-handed helices by changing (*R*) to (*S*) and vice versa.

Analysis of Secondary Structure Preferences of β-Peptides

By combining these substituent effects with the intrinsic stabilities of the secondary structures, we can predict the favored secondary structures for β-peptides with various substitution patterns.

10/12-helix. Since the 10/12-helix has a significant intrinsic preference over all the other secondary structures, a β-peptide should exist in this structure if the substituents do not cause significant destabilization to the structure. The three β-peptides with the 10/12-helix shown in Figure 2 are such cases. First of all, β^3/β-hGly-peptides should favor the 10/12-helix because this type of peptide has an (*S*)-β^3 substituent in its unit 1 and no substituent in its unit 2 (Figure 5). β^2/β^3-peptides should prefer the 10/12-helix because substituents take the (*S*)-β^2 position of unit 2 and the (*S*)-β^3 position of unit 1; both positions are favorable. The unlike-β^3/β^3-peptides also favor the 10/12-helix because the (*S*)-β^3 in unit 1 and the (*R*)-β^3 in unit 2 are favorable positions.

Since the 10/12-helix has four favorable positions for substitutions, namely, (*S*)-β^2 and (*R*)-β^3 positions of unit 1 and (*R*)-β^2 and (*S*)-β^3 positions of unit 2, the types of β-peptides that can exist in this secondary structure may not have been fully realized. Shown in Figure 6 are some other β-peptides that we predict to potentially favor the 10/12-helix. All these β-peptides are in hybrid fashion. These predictions suggest the need for further experimental studies. In this connection, it is remarkable that Kessler et al. reported a 10/12-helix for compound **3**.[80] The hybrid β-peptide is formed by alternative *trans*-5-mr β-amino acid and β-hGly.

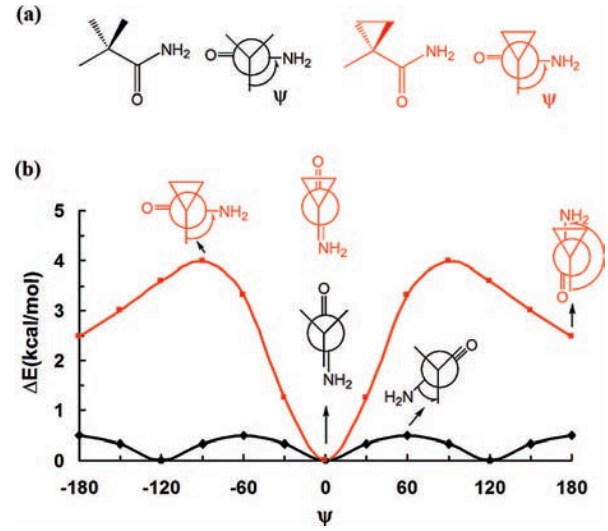
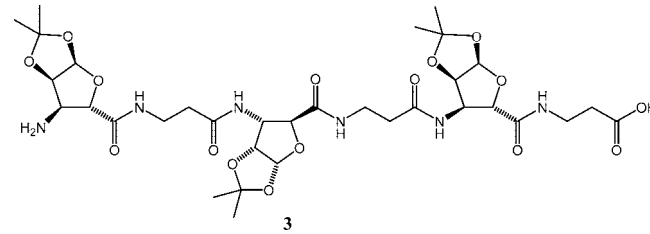


FIGURE 7. Calculated potential energy surfaces of 2,2-dimethylpropanamide and 2-methylcyclopropane carbamide.



3

14-Helix. In the cases of β^3/β-hGly-peptides and β^2/β^3-peptides, the substituent effects are actually somewhat more favorable for the 14-helix over the 10/12-helix. Nevertheless, the 14-helix is not observed because it is intrinsically less stable than the 10/12-helix. However, the experimental observations that β^2-peptides, β^3-peptides, and $\beta^{2,3}$-peptides exist in the 14-helix are supported by the theoretical study. The substituents in these β-peptides significantly stabilize the 14-helix over the other secondary structures as indicated by the results in Figure 5. For example, all these substitution patterns significantly destabilize the 10/12-helix because some substituents will have to be in very unfavorable positions.

12-Helix. Although the 12-helix has a small intrinsic preference over the 14-helix for the unsubstituted β-peptides (Figure 4), the substituent effects considerably favor the 14-helix over the 12-helix. Therefore, the 12-helix is normally unfavorable. However, distinct from other secondary structures, the 12-helix requires a μ-dihedral angle of about 90°. This can be achieved perfectly with a *trans*-ACPC unit with a 30° dihedral angle for the two substituent bonds in the cyclopentane ring.[57]

10-Helix. While other secondary structures favor a μ-dihedral angle of larger than 60°, the 10-helix requires a smaller μ-dihedral angle. This can be achieved by a cis four-membered-ring substitution pattern.[46]

8-Helix. Figure 5 shows that simple alkyl substituents do not favor the 8-helix. However, this is the only structure with the amide carbonyl group gauche to the two C_α−H bonds. When a cyclopropane ring is introduced, there is a strong preference for the C═O to bisect the cyclopropane ring. As shown in Figure 7, two simple amide systems were calculated, one modeling dimethyl substitution and the other modeling cyclopropane substitution. The calculated potential energy surfaces are very different. With dimethyl substitution, there is little conformational preference and the dihedral angle should be very flexible. However, in the cyclopropane case, there is a large preference for the carbonyl group to bisect the cyclopropane ring, which is required for the formation of the 8-helix (see Scheme 1). This conformational preference is mainly due to a hyperconjugative interaction between the cyclopropane and the carbonyl group, instead of due to steric effect.

***β*-Strand and Pleated Sheets.** In unlike-$\beta^{2,3}$-peptides, namely, peptides formed by (2*R*,3*S*) or (2*S*,3*R*) type β-amino acids, all helical structures are destabilized because one of the two substituents has to take an axial position, which interferes with the helix formation. The β-strand, however, does not suffer from this problem.[62] In this case, the two substituents take the two sides of the backbone and are nearly perpendicular to the backbone. Conformational analysis clearly indicates that this is the most favorable conformation.[61,62]

Calculations using dipeptide models indicate that the intrinsic hydrogen bond strength is large for both parallel and antiparallel sheets and affected little by substituents. However, unlike-$\beta^{2,3}$-peptides have much stronger sheet-forming abilities because their backbones are locked in an ideal conformation for sheet formation. Calculations also suggest that sheets have to adopt a twisted geometry (Figure 8a), that is, the β-strand has to be pleated asymmetrically (ψ being larger than ϕ), similar to the β-sheets of α-peptides. This is because a planar or ideally pleated β-strand has a concave geometry (see Figure 4A), which is unfavorable for the formation of sheets. Another interesting finding from the calculations is that there is a large cooperativity in the formation of sheets by β-peptides. This is because all carbonyl groups must be arranged in the same direction, which leads to attractive dipole−dipole interactions between each pair of dipoles as long as they are in different β-strands, as illustrated in Figure 8b. This explains why $\beta^{2,2}$-peptides are observed to be in non-hydrogen-bonded sheet structures in the solid state.[81]

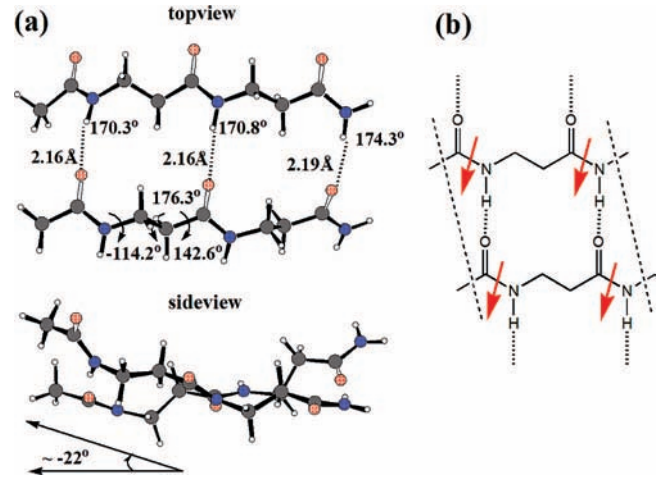


FIGURE 8. The calculated parallel sheet structure of β-peptide and an illustration of cooperativity due to dipole−dipole interactions.

Concluding Remarks

In this paper, the structural features of β-peptides have been discussed. β-Peptides have a strong preference for a gauche N−C_β−C_α−C(═O) dihedral angle due to the electrostatic attraction between N and C(═O). This is an important reason why β-peptides tend to form helical and turn structures. In contrast to α-aminoxy-peptides, β-peptides do not favor an 8-mr hydrogen-bonded local conformation; this allows the formation of 10-, 12-, and 14-mr hydrogen bonds, leading to various secondary structures. The secondary structures of various types of β-peptides were analyzed based on intrinsic backbone conformational preferences and substituent effects. Experimentally observed secondary structures can be well understood. In addition, since the 10/12-helix is found to be the most favorable for the β-peptide backbone, several hybrid peptides shown in Figure 6 are predicted to favor this secondary structure. This should stimulate further experimental studies.

We thank our co-workers, K W. Chan, Yi Ren, Shi-Wei Luo, and Jin-Qiu Lin, for their contributions to the study. We are grateful to the Research Grants Council of Hong Kong and the Natural Science Foundation of China for financial support. Y.D.W. also thanks the Croucher Foundation for a Croucher Senior Research Fellowship award.

BIOGRAPHICAL INFORMATION

Yun-Dong Wu received his B.Sc. from Lanzhou University in 1981 and Ph.D. from University of Pittsburgh in 1986. He had a long association with K. N. Houk, both as a graduate student and as a research associate (shortly with Paul. v. R. Schleyer). In 1992, he joined the Hong Kong University of Science & Technology (HKUST) and is now a Chair Professor of Chemistry. His research group is interested in understanding the mechanisms of cata-

lytic reactions, molecular designs with peptides, modeling of protein folding, and protein/protein interactions.

Wei Han received his B.Sc. in 2002 from Peking University and his Ph.D. from HKUST (with Y.-D. Wu) in 2007. He is currently a postdoctoral fellow in Wu's group. His research interests include conformational studies of polypeptides by quantum calculations, studies of amyloid-β peptide aggregation by molecular dynamics simulations and the development of a coarse-grained protein force field for protein folding simulations.

De-Ping Wang obtained his B.Sc. in Chemistry at Wuhan University in 1992, M.S. in Computer Chemistry at Shanghai Institute of Organic Chemistry, and Ph.D. in Computational Chemistry at HKUST with Y.-D. Wu in 1999. He worked as a postdoctoral associate at Yale University with Professor William Jorgensen. He is currently a scientist at Biogen Idec.

Yi Gao obtained his B.Sc. (Speciality: Biological Chemistry) in 1997 and Ph.D. (Speciality: Theoretical Chemistry) in 2002 at Nanjing University. He worked as a postdoctoral fellow at HKUST (2002−2004) and the University of Nebraska—Lincoln (2004 to present). He has coauthored more than 20 journal articles. He is interested in theoretical studies of structures, functions, and potential applications of biological materials and nanomaterials.

Yi-Lei Zhao received his B.Sc. from University of Science and Technology of China in 1994, M.S. from Peking University (with Chun-Hui Huang) in 1997, and Ph.D. from HKUST with Y.-D. Wu in 2002. After postdoctoral work with Prof. K. N. Houk at UCLA, he joined NIST as a guest researcher with a PM-USA INEST fellowship in 2005. His research focuses on computational chemistry applications in nano- and biotechnology.

FOOTNOTES

*To whom correspondence should be addressed. E-mail: chydwu@ust.hk.

REFERENCES

1 Seebach, D.; Matthews, J. L. β-peptides: A surprise at every turn. *Chem. Commun.* **1997**, 2015–2022.

2 Gellman, S. H. Foldamers: A Manifesto. *Acc. Chem. Res.* **1998**, *31*, 173–180.

3 Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. β-Peptides: From structure to function. *Chem. Rev.* **2001**, *101*, 3219–3232.

4 Seebach, D.; Beck, A. K.; Bierbaum, D. J. The world of β- and γ-peptides comprised of homologated proteinogenic amino acids and other components. *Chem. Biodiversity* **2004**, *1*, 1111–1239.

5 Seebach, D.; Hook, D. F.; Glattli, A. Helices and other secondary structures of β and γ-peptides. *Biopolymers* **2006**, *84*, 23–37.

6 Martinck, T. A.; Fulop, F. Side chain control of β-peptide secondary structures: Design principles. *Eur. J. Biochem.* **2003**, *270*, 3657–3666.

7 Seebach, D.; Abele, S.; Schreiber, J. V.; Martinoni, B.; Nussbaum, A. K.; Schild, H.; Schulz, H.; Hennecke, H; Woessner, R.; Bitsch, F. Biological and pharmacokinetic studies with β-peptides. *Chimia* **1998**, *52*, 734–739.

8 Disney, M. D.; Hook, D. F.; Namoto, K.; Seeberger, P. H.; Seebach, D. N-linked glycosylated β-peptides are resistant to degradation by glycoamidase A. *Chem. Biodiversity* **2005**, *2*, 1624–1634.

9 Seebach, D.; Namoto, K.; Mahajan, Y. R.; Bindschädler, P.; Sustmann, R.; Kirsch, M.; Ryder, N. S.; Weiss, M.; Sauer, M.; Roth, C.; Werner, S.; Beer, H.-D.; Mundling, C.; Walde, P.; Voser, M. Chemical and biological investigations of β-oligoarginines. *Chem. Biodiversity* **2004**, *1*, 65–97.

10 Lind, R.; Greenhow, D.; Perry, S.; Kimmerlin, T.; Seebach, D. Comparative metabolism of α- and β-peptides in the insect *Heliothis virescens* and in plant cells of black mexican sweet maze. *Chem. Biodiversity* **2004**, *1*, 1391–1400.

11 Weiss, H. M.; Wirz, B.; Schweitzer, A.; Amstutz, R.; Rodriguez-Perez, M. I.; res, H.; Metz, Y.; Gardiner, J.; Seebach, D. ADME investigations of unnatural peptides: Distribution of a ^{14}C-labelled β^3-octaarginine in rats. *Chem. Biodiversity* **2007**, *4*, 1413–1437.

12 Porter, E. A.; Wang, X. F.; Lee, H. S.; Weisblum, B.; Gellman, S. H. Antibiotics - non-haemolytic beta-amino-acid oligomers. *Nature* **2000**, *404*, 565.

13 Porter, E. A.; Weisblum, B.; Gellman, S. H. Mimicry of host-defense peptides by unnatural oligomers: Antimicrobial beta-peptides. *J. Am. Chem. Soc.* **2002**, *124*, 7324–7330.

14 Mowery, B. P.; Lee, S. E.; Kissounko, D. A.; Epand, R. F.; Epand, R. M.; Weisblum, B.; Stahl, S. S.; Gellman, S. H. Mimicry of antimicrobial host-defense peptides by random copolymers. *J. Am. Chem. Soc.* **2007**, *129*, 15474–15476.

15 Gademann, K.; Seebach, D. Synthesis of cyclo-β-tripeptides and their biological in vitro evaluation as antiproliferatives against the growth of human cancer cell lines. *Helv. Chim. Acta* **2001**, *84*, 2924–2937.

16 Kritzer, J.; Lear, J. D.; Hodsdon, M. E.; Schepartz, A. Helical β-peptide inhibitors of the p53−hDM2 interaction. *J. Am. Chem. Soc.* **2004**, *126*, 9468–9469.

17 Kritzer, J. A.; Hodsdon, M. E.; Schepartz, A. Solution structure of a β-peptide ligand for hDM2. *J. Am. Chem. Soc.* **2005**, *127*, 4118–4119.

18 Trouche, N.; Wieckowski, S.; Sun, W.; Chaloin, O.; Hoebeke, J.; Fournel, S.; Guichard, G. Small multivalent architectures mimicking homotrimers of the TNF superfamily member CD40L: Delineating the relationship between structure and effector function. *J. Am. Chem. Soc.* **2007**, *129*, 13480–13492.

19 Stephens, O.; Kim, S.; Welch, B. D.; Hodsdon, M. E.; Kay, M. S.; Schepartz, A. Inhibiting HIV fusion with a β-peptide foldamer. *J. Am. Chem. Soc.* **2005**, *127*, 13126–13127.

20 Kritzer, J. S.; Stephens, O. M.; Guarracino, D. A.; Reznik, S. K.; Schepartz, A. β-Peptides as inhibitors of protein-protein interactions. *Bioorg. Med. Chem.* **2005**, *13*, 11–16.

21 Kimmerlin, T.; Namoto, K.; Seebach, D. Evidence from circular dichroism and from melting behavior for helix-inducing complexation of a designed β^3-pentadecapeptide with DNA duplexes. *Helv. Chim. Acta* **2003**, *86*, 2104–2109.

22 Namoto, K.; Gardiner, J.; Kimmerlin, T.; Seebach, D. Investigation of the interactions of β-peptides with DNA duplexes by circular dichroism spectroscopy. *Helv. Chim. Acta* **2006**, *89*, 3087–3103.

23 Gelman, M. A.; Richter, S.; Cao, H.; Umezawa, N.; Gellman, S. H.; Rana, T. M. Selective binding of TAR RNA by a Tat-derived β-peptide. *Org. Lett.* **2003**, *5*, 3563–3565.

24 Shimanouchi, T.; Walde, P.; Gardiner, J.; Mahajan, Y. R.; Seebach, D.; Thomae, A.; Kramer, S. D.; Voser, M.; Kuboi, R. Permeation of a β-heptapeptide derivative across phospholipid bilayers. *Biochim. Biophys. Acta: Biomembr.* **2007**, *1768*, 2726–2736.

25 Lelais, G.; Micuch, P.; Josien-Lefebre, D.; Rossi, F.; Davies, S. G.; Seebach, D. Preparation of protected β^2- and β^3-homocysteine, β^2- and β^3-homohistidine and β^2-homoserine for solid-phase synthesis. *Helv. Chim. Acta* **2004**, *87*, 3131–3159.

26 Seebach, D.; Abele, S.; Gademann, K.; Guichard, G.; Hintermann, T.; Jaun, B.; Mathews, J. L.; Schreiber, J. V.; Oberer, L.; Hommel, U.; Widmer, H. β^2- and β^3-Peptides with proteinaceous side chains: Synthesis and solution structures of constitutional isomers, a novel helical secondary structure and the influence of solvation and hydrophobic interactions on folding. *Helv. Chim. Acta* **1998**, *81*, 932–987.

27 Davies, S. G.; Garrido, N. M.; Kruchinin, D.; Ichihara, O.; Kotchie, L. J.; Price, P. D.; PriceMortimer, A. J.; Russell, A. J.; Smith, A. D. Homochiral lithium amides for the asymmetric synthesis of β-amino acids. *Tetrahedron: Asymmetry* **2006**, *17*, 1793–1811.

28 Lelais, G.; Seebach, D. β^2-Amino acids - syntheses, occurance in natural products, and components of β-peptides. *Biopolymers* **2004**, *76*, 206–243.

29 Seebach, D.; Overhand, M.; Kühnle, F. N. M.; Martinoni, B.; Oberer, L.; Hommel, U.; Widmer, H. β-peptides: Synthesis by Arndt-Eistert homologation with concomitant peptide coupling. Structure determination by NMR and CD spectroscopy and by X-ray crystallography. Helical secondary structure of a β-hexapeptide in solution and its stability towards pepsin. *Helv. Chim. Acta* **1996**, *79*, 913–941.

30 Appella, D. H.; Christianson, L. A.; Karle, I. L.; Powell, D. R.; Gellman, S. H. β-peptide foldamers: Robust helix formation in a new family of β-amino acid oligomers. *J. Am. Chem. Soc.* **1996**, *118*, 13071–13072.

31 Appella, D. H.; Barchi, J. J. J.; Durrell, S. R.; Gellman, S. H. Formation of short, stable helices in aqueous solution by β-amino acid hexamers. *J. Am. Chem. Soc.* **1999**, *121*, 2309–2310.

32 Appella, D. H.; Christianson, L. A.; Karle, I. L.; Powell, D. R.; Gellman, S. H. Synthesis and characterization of *trans*-2-aminocyclohexanecarboxylic acid oligomers: An unnatural helical secondary structure and implications for β-peptide tertiary structure. *J. Am. Chem. Soc.* **1999**, *121*, 6206–6212.

33 Barchi, J. J. J.; Huang, X.; Appella, D. H.; Christianson, L. A.; Durell, S. R.; Gellman, S. H. Solution conformations of helix-forming β-amino acid homooligomers. *J. Am. Chem. Soc.* **2000**, *122*, 2711–2718.

34 Raguse, T. L.; Lai, J. R.; Gellman, S. H. Evidence that the β-peptide 14-helix is stabilized by β^3-residues with side-chain branching adjacent to the β-carbon atom. *Helv. Chim. Acta* **2002**, *85*, 4154–4164.

35 Etezady-Esfarjani, T.; Hilty, C.; Wüthrich, K.; Rueping, M.; Schreiber, J. V.; Seebach, D. NMR-structural investigations of a β^3-dodecapeptide with proteinogenic side chains in methanol and in aqueous solutions. *Helv. Chim. Acta* **2002**, *85*, 1197–1209.

36 Hart, S. A.; Bahadoor, A. B. F.; Matthews, E. E.; Qiu, X. J.; Schepartz, A. Helix macrodipole control of β^3-peptide 14-helix stability in water. *J. Am. Chem. Soc.* **2003**, *125*, 4022–4023.

37 Seebach, D.; Mathad, R. I.; Kimmerlin, T.; Mahajan, Y. R.; Bindschädler, P.; Rueping, M.; Jaun, B.; Hilty, C.; Etezady-Esfarjani, T. NMR-solution structures in methanol of an α-heptapeptide, of a β^3/β^2-nonapeptide, and of an all-β^3-icosapeptide carrying the 20 proteinogenic side chains. *Helv. Chim. Acta* **2005**, *88*, 1969–1982.

38 Seebach, D.; Jacobi, A.; Rueping, M.; Gademann, K.; Ernst, M.; Jaun, B. Synthesis of β-hexa- and β-heptapeptides containing novel $\beta^{2,3}$-amino acids with two serine or two cysteine side chains - CD- and NMR-spectroscopic evidence for 3(14)-helical secondary structures in water. *Helv. Chim. Acta* **2000**, *83*, 2115–2140.

39 Seebach, D.; Gademann, K.; Schreiber, J. V.; Matthews, J. L.; Hintermann, T.; Jaun, B.; Oberer, L.; Hommel, U.; Widmer, H. 'Mixed' β-peptides: A unique helical secondary structure in solution. *Helv. Chim. Acta* **1997**, *80*, 2033–2038.

40 Rueping, M.; Schreiber, J. V.; Lelais, G.; Jaun, B.; Seebach, D. Mixed β^2/β^3-hexapeptides and β^2/β^3-nonapeptides folding to (P)-helices with alternating twelve- and ten-membered hydrogen-bonded rings. *Helv. Chim. Acta* **2002**, *85*, 2577–2593.

41 Sharma, G. V. M.; Reddy, K. R.; Krishna, P. R.; Sankar, A. R.; Jayaprakash, P.; Jagannadh, B.; Kunwar, A. C. Left-handed helical twists in mixed peptides derived from alternating C-linked carbo-β^3-amino acids and β-hGly units. *Angew. Chem., Int. Ed.* **2004**, *43*, 3961–3965.

42 Appella, D. H.; Christianson, L. A.; Klein, D. A.; Powell, D. R.; Huang, X.; Barchi, J. J.; Gellman, S. H. Residue-based control of helix shape in β-peptide oligomers. *Nature* **1997**, *387*, 381–384.

43 Appella, D. H.; Christianson, L. A.; Klein, D. A.; Richards, M. R.; Powell, D. R.; Gellman, S. H. Synthesis and structural characterization of helix-forming β-peptides: *trans*-2-Aminocyclopentanecarboxylic acid oligomers. *J. Am. Chem. Soc.* **1999**, *121*, 7574–7581.

44 Woll, M. G.; Fisk, J. D.; LePlae, P. R.; Gellman, S. H. Stereoselective synthesis of 3-substituted 2-aminocyclopentanecarboxylic acid derivatives and their incorporation into short 12-helical β-peptides that fold in water. *J. Am. Chem. Soc.* **2002**, *124*, 12447–12452.

45 Park, J.-S.; Lee, H.-S.; Lai, J. R.; Kim, B. M.; Gellman, S. H. Accommodation of α-substituted residues in the β-peptide 12-helix: Expanding the range of substitution patterns available to a foldamer scaffold. *J. Am. Chem. Soc.* **2003**, *125*, 8539–8545.

46 Claridge, T. D. W.; Goodman, J. M.; Moreno, A.; Angus, D.; Barker, S. F.; Taillefumier, C.; Watterson, M. P.; Fleet, G. W. J. 10-Helical conformations in oxetane β-amino acid hexamers. *Tetrahedron Lett.* **2001**, *42*, 4251–4255.

47 Seebach, D.; Abele, S.; Sifferlen, T.; Hänggi, M.; Gruner, S.; Seiler, P. Preparation and structure of β-peptides consisting of geminally disubstituted $\beta^{2,2}$- and $\beta^{3,3}$-amino acids: A turn motif for β-peptides. *Helv. Chim. Acta* **1998**, *81*, 2218–2243.

48 Abele, S.; Seiler, P.; Seebach, D. Synthesis, crystal structures, and modelling of β-oligopeptides consisting of 1-(aminomethyl)cyclopropanecarboxylic acid: Ribbon-type arrangement of eight-membered H-bonded rings. *Helv. Chim. Acta* **1999**, *82*, 1559–1571.

49 Doerksen, R. J.; Chen, B.; Yuan, J.; Winkler, J. D.; Klein, M. L. Novel conformationally-constrained β-peptides characterized by H-1 NMR chemical shifts. *Chem. Commun.* **2003**, *20*, 2534–2535.

50 Gademann, K.; Häne, A.; Rueping, M.; Jaun, B.; Seebach, D. The fourth helical secondary structure of β-peptides: The (P)-2(8)-helix of a β-hexapeptide consisting of (2*R*,3*S*)-3-amino-2-hydroxy acid residues. *Angew. Chem., Int. Ed.* **2003**, *42*, 1534–1537.

51 Peter, C.; Rueping, M.; Worner, H. J.; Jaun, B. Molecular dynamics simulations of small peptides: can one derive conformational preferences from ROESY spectra. *Chem.—Eur. J.* **2003**, *9*, 5838–5849.

52 Krauthäuser, S.; Christianson, L. A.; Powell, D. R.; Gellman, S. H. Antiparallel sheet formation in β-peptide foldamers: Effects of β-amino acid substitution on conformational preference. *J. Am. Chem. Soc.* **1997**, *119*, 11719–11720.

53 Chung, Y. J.; Christianson, L. A.; Stanger, H. E.; Powell, D. R.; Gellman, S. H. A β-peptide reverse turn that promotes hairpin formation. *J. Am. Chem. Soc.* **1998**, *120*, 10555–10556.

54 Seebach, D.; Abele, S.; Gademann, K.; Jaun, B. Pleated sheets and turns of β-peptides with proteinogenic side chains. *Angew. Chem., Int. Ed.* **1999**, *38*, 1595–1597.

55 Daura, X.; Gademann, K.; Schäfer, H.; Jaun, B.; Seebach, D.; van Gunsteren, W. F. The β-peptide hairpin in solution: Conformational study of a β-hexapeptide in methanol by NMR spectroscopy and MD simulation. *J. Am. Chem. Soc.* **2001**, *123*, 2393–2404.

56 Langenhan, J. M.; Gellman, S. H. Effects of alternative side chain pairings and reverse turn sequences on antiparallel sheet structure in β-peptide hairpins. *Org. Lett.* **2004**, *6*, 937–940.

57 Langenhan, J. M.; Guzei, I. A.; Gellman, S. H. Parallel sheet secondary structure in β-peptides. *Angew. Chem., Int. Ed.* **2003**, *42*, 2402–2405.

58 Wu, Y.-D.; Wang, D.-P. Theoretical studies of β-peptide models. *J. Am. Chem. Soc.* **1998**, *120*, 13485–13493.

59 Wu, Y.-D.; Wang, D.-P. Theoretical studies on the side-chain control of 14-helix and 10/12-mixed helix of β-peptides. *J. Am. Chem. Soc.* **1999**, *121*, 9352–9362.

60 Wu, Y.-D.; Lin, J.-Q.; Zhao, Y.-L. Theoretical study of poly-β-alanine models: Intrinsic preferences of helical structures. *Helv. Chim. Acta* **2002**, *85*, 3144–3160.

61 Lin, J.-Q.; Luo, S.-W.; Wu, Y.-D. Theoretical study on the β-sheets formed by β-peptides. *J. Comput. Chem.* **2002**, *23*, 1551–1558.

62 Wu, Y.-D.; Wang, D.-P. Conformational features of $\beta^{2,3}$-peptide. *J. Chin. Chem. Soc.* **2000**, *47*, 129–134.

63 Möhle, K.; Günther, R.; Thormann, M.; Sewald, N.; Hofmann, H.-J. Basic conformers in β-peptides. *Biopolymers* **1999**, *50*, 167–184.

64 Günther, R.; Hofmann, H.-J.; Kuczera, K. Searching for periodic structures in β-peptides. *J. Phys. Chem. B* **2001**, *105*, 5559–5567.

65 Günther, R.; Hofmann, H.-J. Theoretical prediction of substituent effects on the intrinsic folding properties of β-peptides. *Helv. Chim. Acta* **2002**, *85*, 2149–2168.

66 Baldauf, C.; Gunther, R.; Hofmann, H.-J. Mixed helices - A general folding pattern in homologous peptides. *Angew. Chem., Int. Ed.* **2004**, *42*, 1594–1597.

67 Baldauf, C.; Gunther, R.; Hofmann, H.-J. Side-chain control of folding of the homologous alpha-, beta-, and gamma-peptides into "mixed" helices (beta-helices). *Biopolymers* **2005**, *80*, 675–687.

68 Daura, X.; Gademann, K.; Jaun, B.; Seebach, D.; van Gunsteren, W. F.; Mark, A. E. Peptide folding: When simulation meets experiment. *Angew. Chem., Int. Ed.* **1999**, *38*, 236–240.

69 Daura, X.; Jaun, B.; Seebach, D.; van Gunsteren, W. F.; Mark, A. E. Reversible peptide folding in solution by molecular dynamics simulation. *J. Mol. Biol.* **1998**, *280*, 925–932.

70 Seebach, D.; Schreiber, J. V.; Abele, S.; Daura, X.; van Gunsteren, W. F. Structure and conformation of β-oligopeptide derivatives with simple proteinogenic side chains: Circular dichroism and molecular dynamics investigations. *Helv. Chim. Acta* **2000**, *83*, 34–57.

71 van Gunsteren, W. F.; Bürgi, R.; Peter, C.; Daura, X. The key to solving the protein-folding problem lies in an accurate description of the denatured state. *Angew. Chem., Int. Ed.* **2001**, *40*, 351–355.

72 Baron, R.; Bakowies, D.; van Gunsteren, W. F.; Daura, X. β-peptides with different secondary-structure preferences: How different are their conformational spaces. *Helv. Chim. Acta* **2002**, *85*, 3872–3882.

73 Glättli, A.; Daura, X.; Seebach, D.; van Gunsteren, W. F. Can one derive the conformational preference of a β-peptide from its CD spectrum? *J. Am. Chem. Soc.* **2002**, *124*, 12972–12978.

74 Daura, X.; Glättli, A.; Gee, P.; Peter, C.; van Gunsteren, W. F. Unfolded state of peptides. *Adv. Protein Chem.* **2002**, *62*, 341–360.

75 Glättli, A.; Seebach, D.; van Gunsteren, W. F. Do valine side chains have an influence on the folding behavior of β-substituted β-peptides? *Helv. Chim. Acta* **2004**, *87*, 2487–2506.

76 Trzesniak, D.; Glättli, A.; Jaun, B.; van Gunsteren, W. F. Interpreting NMR data for β-peptides using molecular dynamics simulations. *J. Am. Chem. Soc.* **2005**, *127*, 14320–14329.

77 Glättli, A.; Daura, X.; Bindschädler, P.; Jaun, B.; Mahajan, Y. R.; Mathad, R. I.; Rueping, M.; Seebach, D.; van Gunsteren, W. F. On the influence of charged side chains on the folding-unfolding equilibrium of beta-peptides: A molecular dynamics simulation study. *Chem.—Eur. J.* **2005**, *11*, 7276–7293.

78 Wu, Y. D.; Wang, D. P.; Chan, K. W. K.; Yang, D. Theoretical study of peptides formed by aminoxy acids. *J. Am. Chem. Soc.* **1999**, *121*, 11189–11196.

79 Li, X.; Yang, D. Peptides of aminoxy acids as foldamers. *Chem. Commun.* **2006**, 3367–3379.

80 Gruner, S. A. W.; Truffault, V.; Voll, G.; Locardi, W.; Stöckle, M.; Kessler, H. Design, synthesis, and NMR structure of linear and cyclic oligomers containing novel furanoid sugar amino acids. *Chem.—Eur. J.* **2002**, *8*, 4366–4376.

81 Seebach, D.; Sifferlen, T.; Bierbaum, D. J.; Rueping, M.; Jaun, B.; Schweizer, B.; S chaefer, J.; Mehta, A. K.; O'Connor, R. D.; Meier, B. H.; Ernst, M.; Glättli, A. Isotopically labelled and unlabelled, β-peptides with geminal dimethyl substitution in 2-position of each residue: Synthesis and NMR investigation in solution and in the solid state. *Helv. Chim. Acta* **2002**, *85*, 2877–2917.