Theoretical Studies of β-Peptide Models

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Received June 3, 1998. Revised Manuscript Received October 8, 1998

Abstract: The key conformations of β-dipeptide models **4**−**9** have been studied with quantum mechanics calculations including a self-consistent isodensity solvation model to evaluate the tendency of β-sheet, 14-helix, and 12-helix formation of β-peptide models. The most stable conformation of dipeptide models **5**−**7** is a formal six-membered-ring (C6) hydrogen-bonded structure, although the hydrogen bond is very weak because of a bad N−H- - -O angle. Many local conformational minima with folded structures are found. This is attributed to internal non-hydrogen-bonded electrostatic (or dipole) interactions. Most interestingly, for dipeptide model **7**, the most stable conformation in polar solvent is predicted to correspond to the 14-helix. The conformations for β-sheet, 14-helix, and 12-helix are much destabilized by electrostatic interactions in the gas phase but significantly benefit from the polar solvent effect. The 12-helix is intrinsically less favorable than the 14-helix. The key difference between 14- and 12-helices is the dihedral angle (μ) about the $C_\alpha-C_\beta$ bond—the former is about 60° while the latter is about 90°. Comparatively, β^3-peptides have greater 14-helical propensity than β^2-peptides. The five-membered and six-membered rings in dipeptide models **8** and **9** promote the 12-helix and 14-helix conformations, respectively. Calculations for β-hexapeptide models **10** and **11** indicate somewhat stronger hydrogen bonding in the 12-helix than in the 14-helix structure.

Introduction

Recently, the β-peptides, which consist entirely of β-amino acids instead of α-amino acids, have received intensive attention because of their interesting secondary structures.[1−3] Depending upon side chain substitution patterns, β-sheet, 14-helix, and 12-helix all have been observed.[1] Due to the great variety of substitution patterns, the ease of the formation of secondary structures with even four to six residues compared to about 15 for natural peptides, and ready formation of cyclic compounds that stack into tube structures,[5] β-peptides have generated great excitement.[6] In addition, β-amino acids also frequently occur in natural products, especially cyclic peptides.[7] It has been found that β-amino acids have excellent stability toward proteases.[3] Therefore, they have wide applications in drug development.[8]

At first, the study of the secondary structure of β-peptides was carried out on poly(β-alanine) and polymers derived from β-amino acids (the so-called Nylon-3 derivatives).[9,10] In 1984, Subirana et al. observed an α-helical conformation for poly(α-isobutyl L-aspartate).[11] On the basis of the X-ray diffraction patterns of these polymers and conformational analyses, they proposed secondary structures including 14-, 16-, 18-, and 20-helices.[11−14] However, recently, Seebach et al. reported a series of β-peptides with different alkyl substitution patterns. They found a 3_1-helical structure (14-helix) to be a common structure

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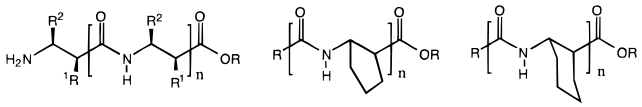
10.1021/ja981939b CCC: $15.00
Published on Web 12/09/1998

for β-peptides with all α-substituted (**1**, $R_2 = H$) β-amino acids, β^2-peptide, or all β-substituted (**1**, $R_1 = H$) β-amino acids, β^3-peptide.[1,3] At the same time, Gellman's group reported that β-peptides **2**, with trans-substituted cyclohexane rings, strongly favor a 14-helix structure[2a,15] while β-peptides **3**, with *trans*-



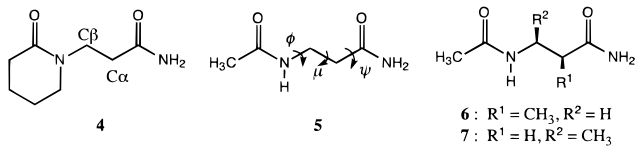
1 R^1 or R^2 = alkyl **2** **3**

substituted cyclopentane rings, adopt a helical structure with 12-membered-ring hydrogen bonds (12-helix).[2b,16] More recently, another unusual helical structure was reported by Seebach et al. for several peptides with mixed α- and β-alkyl substitutions. This structure is proposed to exist in a 12/10/12 sequence of hydrogen-bonding pattern.[4]

A β-amino acid chain introduces additional degrees of conformational flexibility because of the possible rotation around the $C_\alpha-C_\beta$ single bond (this dihedral angle is usually called the μ angle).[7b] The easy formation of secondary structures for β-peptides is totally unexpected because they have greater flexibility. Therefore, there should be special local geometrical preferences that facilitate the folding of β-peptides.

The conformational preferences of α-peptides have been widely studied.[17,18] Previous theoretical calculations often used dipeptide models. Ab initio calculations for glycine dipeptide and alanine dipeptide indicated that the conformational variations of these two dipeptides are similar to those in proteins and, therefore, can be considered as reasonable models of the larger globular proteins.[17a]

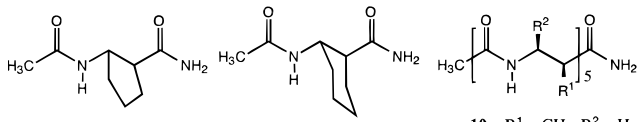
On the other hand, model study of conformational features of β-peptides is limited. Gellman et al. reported an IR and NMR study of conformational preferences of dipeptides **4** and **5**. They found that an eight-membered-ring (C8) rigid conformation is unfavorable for **5**.[19] For compound **4**, a C8 conformation exists



4 **5** **6**: $R^1 = CH_3, R^2 = H$; **7**: $R^1 = H, R^2 = CH_3$

in equilibrium with an extended conformation. As far as we are aware, there has been only one theoretical study on β-peptide model **5** with a molecular mechanics method.[20] Ab initio calculations on a conformational feature of β-alanine have been performed.[21,22] However, the system is too small to understand the general conformational features of β-peptides. Molecular dynamics methods have been applied to predict the folding patterns of β-peptides.[2,23] These simulations used molecular mechanics force fields, and promising results have been obtained. For example, prediction was made about the helical structure of compound **3**, which was consequently confirmed by experiment.[2b,15]

In this paper, we report our ab initio quantum mechanics study on peptide models **4**−**11**. We focus our attention on locating



8 **9** **10**: $R^1 = CH_3, R^2 = H$; **11**: $R^1 = H, R^2 = CH_3$

low-energy conformations and the conformations associated with the formation of secondary structures and polar solvent effect on the conformational preferences. We show that the local structures of β-peptides that lead to the β-sheet and helices are much higher in energy than the most favorable conformation in the gas phase but are significantly stabilized by the solvent effect; substituents have a considerable effect on the conformational preference of the peptide backbone; the 12-helix usually is less stable than the 14-helix except for some special cases. In addition, we hope that the current results can be used for the modification of molecular mechanics force fields for the calculation of β-amino acid related systems.

Computational Methodology

Structures of β-peptide models **4**−**9** were optimized by the HF/6-31G** method using the GAUSSIAN94 program.[24] All the stationary points were characterized by harmonic vibrational frequency calculations. Single-point MP2 calculations were performed on the HF/6-31G**-optimized conformations with the same basis set.

To investigate the solvent effect on conformational preference of dipeptide models **4**−**9**, the self-consistent isodensity surface polarized continuum model (SCIPCM)[25] was employed to evaluate the solvation energy at the HF/6-31G** level. The SCIPCM follows the philosophy of the polarized continuum models of Tomasi et al.[26] but uses a cavity which is defined through a self-consistently optimized surface of

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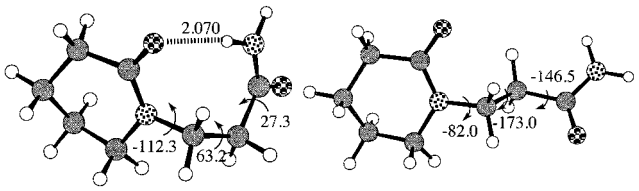

4a **4b**

	Gas	Solv			Gas	Solv		
isosurface		0.001	0.0008	0.0004		0.001	0.0008	0.0004
HF/6-31G**	0.0	0.9	0.6	0.2	0.6	0.0	0.0	0.0
MP2/6-31G**	0.0	0.0	0.0	0.0	2.8	1.4	1.6	1.9
B3LYP/6-31G**	0.0	0.0	0.0	0.0	2.4	1.0	1.2	1.5
Experiment		0.0				1.4		

Figure 1. Calculated conformers of dipeptide model **4** and their relative enthalpies. Three isosurface values (au) were used in the solvation calculation.

constant electron density.[27] There has already been ample evidence to suggest that this method is superior to simple Onsager-based methods.[28] To avoid the risk of artifacts of defining cavity, three values, 0.001, 0.0008, and 0.0004 au, were used as the isosurface values for structure **4**. For structures **5**−**9**, the SCIPCM calculations were performed with two dielectric constants of $\epsilon = 8.0$ for CH_2Cl_2 and $\epsilon = 33.0$ for CH_3OH with an isosurface value of 0.0008. To compare our results with existing experimental results, the solvation calculations for compound **4** were also carried out with the MP2/6-31G** method[29] and the nonlocal density functional B3LYP/6-31G** method of density functional theory.[30]

For β-hexapeptide models **10** and **11**, geometries were optimized with the HF/6-31G* method and energies were calculated with the B3LYP/6-31G* method.

Results and Discussion

Dipeptide Model 4. We first carried out the calculations on dipeptide model **4** using different methods. The solution conformation of **4** was studied by Dado and Gellman using NMR and IR methods.[19a] Two equilibrating conformers, a hydrogen-bonded conformer, and an extended conformer were deduced in CH_2Cl_2. The former is enthalpically more favorable by about 1.4 kcal/mol but with an entropy about 5.8 eu smaller than the latter.[19a] The calculated conformers are shown in Figure 1. **4a** is in a C8 hydrogen-bonded structure with an O- - -H distance of 2.07 Å. Enthalpically, it is 0.6, 2.8, and 2.4 kcal/mol more stable than **4b** by HF/6-31G**, MP2/6-31G**, and B3LYP/6-31G** calculations, respectively. As expected, the correlation energy correction considerably stabilizes the C8 conformer. The HF/6-31G** calculations also indicated that conformer **4a** has an entropy of about 5.2 eu less than conformer **4b**, in close agreement with the value of 5.8 eu observed experimentally.[19a] When the solvation model ($\epsilon = 8.0$ for CH_2Cl_2) was applied, we observed the following (Figure 1): (1) Solvation considerably stabilizes (0.9−1.4 kcal/mol) conformer **4b** relative to **4a**. (2) The relative stabilization of **4b** is almost independent of the method of calculation (HF, MP2, or B3LYP). (3) The relative stabilization of **4b** is sensitive to the isosurface value—the larger the isosurface value, the greater the stabilization to **4b**. Thus, from 0.0004 to 0.001, the stabilization of **4b** increases by about 0.5 kcal/mol.

It should be noted that, because the solvent lacks structure in the SCIPCM, the model is not very appropriate for solvents that have important specific interactions (like hydrogen bonds) with the solute.[27,28] It does, however, give a good prediction for the solvent without hydrogen bond donors and hydrogen bond acceptors such as CH_2Cl_2 for our peptide system. The sensitivity of the calculated relative solvation effect to the isosurface value is a weakness of the current model. The default value in the GAUSSIAN 94 is 0.0004 au. A comparison between the results and the experimental value indicates that an isosurface value of 0.0008 may work better for our current system. Thus, for the calculation of dipeptide models **5**−**9**, the isosurface of 0.0008 au was used. Because the solvent effect is almost independent of the calculation method, in our further study, the solvation model was only applied with the HF/6-31G** calculation. Relative enthalpies of conformers were calculated by the MP2/6-31G** gas-phase enthalpies corrected by the HF/6-31G** solvation energies.

Dipeptide Model 5. With an additional methylene group in the backbone compared to the glycine dipeptide analogue, there are three rotatable single bonds. A systematic conformational search with 15° increments for the three dihedral angles ϕ, μ, and ψ would mean the calculation of 13 824 structures. This is impractical. Therefore, instead of exploring the whole potential energy surface, we focused our attention on locating all conformational minima with low energies and conformations significant for secondary structures. Conformations with cis peptide units were excluded because each unit would cost about 2.5 kcal/mol.[31] For compound **5**, six minima were located, as shown in Figure 2. The summary of dihedral angles and energetics of these conformers is given in Table 1.

Before discussing the energetics of conformers **5a**−**f** in Figure 2, it is beneficial to review the conformational preferences about the dihedral angles ϕ, μ, and ψ. Model calculations by Maxwell et al. using the HF/6-31G* method indicate the following:[32] For *N*-ethylformamide, the most stable conformation has a near perpendicular C−N−C−C dihedral angle ($\phi = 88°$). However, the potential energy surface is quite flat in the range $\phi = 90-270°$, with a barrier of about 0.5 kcal/mol at $\phi = 180°$. For propanamide, the most stable conformation is $\psi = 180°$ (methyl eclipses with C═O) and the least stable conformation is $\psi = 0°$, which is higher in energy by 1.6 kcal/mol. The preference for μ has not been studied. As will be discussed latter, there might be a preference for gauche over anti.

At each level of calculation, conformer **5a** is predicted to be most stable. In this conformer, dihedral angles ϕ (89°) and ψ (179°) are the most favorable values while dihedral angle μ (63°) is gauche. Although this is formally a six-membered-ring conformer, referred to as C6, the hydrogen bonding is weak, as indicated by the following: the H- - -N distance is large (2.46 Å), the N−H- - -O angle is too small (108°), and the N−H bond length is a little elongated. Nevertheless, this structure is stabilized by electrostatic attraction. Conformer **5c** can be derived from **5a** by rotating the dihedral angle μ from gauche to anti. This structure is less stable than **5a** by about 3 kcal/mol in the gas phase but is calculated to be 1.3−1.6 kcal/mol less stable in solution conditions.

Both conformers **5b** and **5d** form C8 hydrogen-bonded structure. Despite a strong hydrogen bond in **5b**, the conformer is still less stable than **5a** enthalpically. The major reason that **5b** is less stable than **5a** is the former's unfavorable dihedral

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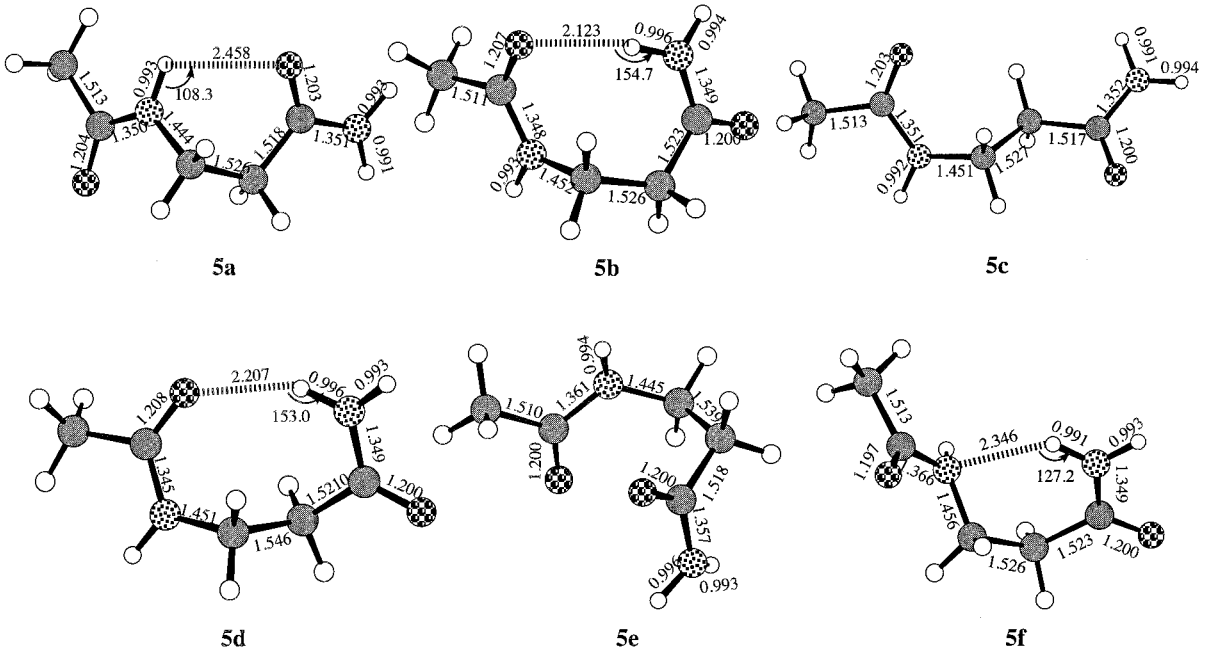

Figure 2. HF/6-31G**-optimized minima of β-dipeptide model **5**: **5a**, C6 conformer; **5b**,**d**, C8 conformers; **5c**, extended conformer.

Table 1. Calculated Dipole Moments, Torsional Angles, Entropies, Relative Enthalpies in the Gas Phase, and Relative Enthalpies and Free Energies (298 K) in Solution for the Conformational Minima of β-Dipeptide Models **5**−**9**[a]

							solv SCIPCM model			
	gas phase						ΔH[d]		ΔG[e]	
conformer	dipole (D)	ϕ	μ	ψ	S[b]	ΔH[c]	$\epsilon = 8.0$	$\epsilon = 33.0$	$\epsilon = 8.0$	$\epsilon = 33.0$
					Dipeptide Model **5**					
5a	3.3	88.5	62.8	−179.1	103.5	0.0	0.0	0.0	0.0	0.0
5b	4.8	−110.8	64.5	23.8	100.0	0.9	0.2	0.1	1.2	1.1
5c	3.1	−76.1	−174.3	−152.7	103.9	3.1	1.7	1.4	1.6	1.3
5d	5.9	−73.5	135.8	−67.0	101.4	1.9	1.7	1.7	2.3	2.3
5e	2.8	−92.8	52.0	89.2	99.1	2.7	2.6	2.5	3.9	3.8
5f	4.4	−165.9	72.1	−19.6	103.1	4.9	2.7	2.2	2.8	2.3
					Dipeptide Model **6**					
6a	2.6	85.5	57.6	−158.2	109.3	0.0	0.0	0.0	0.0	0.0
6b	4.4	−113.8	−66.8	−156.6	108.8	−0.1	0.1	0.2	0.2	0.3
6c	4.4	−112.7	60.0	29.5	105.8	0.3	0.0	−0.2	1.0	0.8
6d	4.8	113.2	−65.5	−24.2	105.3	0.2	0.4	0.4	1.6	1.6
6e	6.2	105.9	170.3	155.8	109.4	4.2	2.3	1.7	2.3	1.7
6f	2.3	103.9	168.9	118.2	109.2	4.0	2.8	2.5	2.8	2.5
6g	3.0	93.9	−54.2	−86.9	104.9	1.6	1.7	1.6	3.0	2.9
6h	6.8	−117.4	73.6	−85.5	108.4	4.3	2.0	1.2	2.3	1.5
					Dipeptide Model **7**					
7a	5.0	−138.9	−62.5	−153.2	108.3	0.0	0.0	0.0	0.0	0.0
7b	3.8	−160.8	55.6	100.6	108.2	1.5	1.3	1.2	1.3	1.2
7c	4.5	−111.8	59.0	29.7	105.6	0.6	−0.2	−0.3	0.6	0.5
7d	1.8	62.8	61.0	−167.0	108.0	1.4	1.3	1.4	1.4	1.5
7e	2.7	53.7	50.5	−115.2	105.8	1.0	1.1	1.0	1.8	1.7
7f	2.4	−61.6	−44.9	110.2	106.1	0.8	1.2	1.3	1.9	2.0
7g	4.7	−75.1	168.4	178.7	110.6	3.1	2.1	1.7	1.4	1.0
7h	1.9	61.3	162.2	157.0	108.2	3.3	2.5	1.9	2.5	1.9
7i	2.8	−93.4	50.2	89.0	105.4	2.2	2.2	2.2	3.1	3.1
7j	7.1	−154.7	64.3	−135.9	110.3	4.5	1.4	0.3	0.8	−0.3
					Dipeptide Model **8**					
8a	5.7	−74.3	127.9	−68.3	109.7	0.0	0.0	0.0	0.0	0.0
8b	5.5	−151.0	90.7	−62.6	112.7	5.0	2.9	2.4	2.0	1.5
					Dipeptide Model **9**					
9a	2.8	54.6	52.9	−114.0	113.9	0.0	0.0	0.0	0.0	0.0
9b	6.7	−154.8	59.0	−120.7	116.9	3.2	0.4	−0.4	−0.5	−1.3

[a] Geometries optimized at the HF/6-31G** level. [b] Entropy in cal/(mol K). [c] MP2/6-31G** single-point energy plus thermal energy correction in kcal/mol. [d] MP2/6-31G** single-point energy plus solvent effect and thermal energy correction ($\Delta H = \Delta H_{MP2/gas} + \Delta(E_{HF/sol} - E_{HF/gas})$) in kcal/mol. [e] Free energy based on ΔH in solution and ΔS in the gas phase in kcal/mol.

angle ψ (−23°). This causes about 1.5 kcal/mol destabilization.[33] Conformer **5d** has less problem with ψ but is considerably destabilized by the partial eclipsing about the central $C_\alpha-C_\beta$ bond ($\mu = 136°$). Conformer **5e** differs from **5b** mainly in the dihedral angle ψ. This conformer is quite high in energy because of the loss of hydrogen bonding. Conformer **5f** is least stable in the gas phase. It differs from **5b** mainly in the ϕ angle, which also causes the loss of hydrogen bonding.

Conformers **5b** and **5c** correspond to conformers **4a** and **4b**, respectively. The calculation results for the two compounds (**4**

Table 2. Calculated Dipole Moments, Torsional Angles, and Relative Energies (kcal/mol) of C6 (**A**), β-Sheet (**B**), 14-Helix (**C**), and 12-Helix (**D**) Conformers of β-Dipeptide Models **5**−**7**

						solv SCIPCM model	
	gas phase					ΔE^b	
conformer	dipole (D)	ϕ	μ	ψ	ΔE^a	$\epsilon = 8.0$	$\epsilon = 33.0$
			5, R1 = H, R2 = H				
A	3.3	88.5	62.8	−179.1	0.0	0.0	0.0
B (β-sheet)	7.7	180.0	180.0	180.0	6.6	2.9	2.0
	7.5	120.0	180.0	−120.0	6.0	3.0	2.3
C (14-helix)	7.2	−154.7	64.3	−135.9	5.8	2.7	1.8
D (12-helix)	6.7	−90.0	89.0	−110.0	5.9	3.9	3.2
			6, R1 = CH3, R2 = H				
A	2.6	85.5	57.6	−158.2	0.0	0.0	0.0
B (β-sheet)	7.4	180.0	180.0	180.0	7.0	3.9	3.0
	7.3	120.0	180.0	−120.0	4.6	2.2	1.5
C (14-helix)	7.2	−154.7	64.3	−135.9	5.1	1.6	1.1
D (12-helix)	6.6	−90.0	89.0	−110.0	5.0	3.1	2.4
			7, R1 = H, R2 = CH3				
A	5.0	138.9	62.5	153.2	0.0	0.0	0.0
B (β-sheet)	7.2	180.0	180.0	180.0	7.3	5.4	4.7
	7.4	120.0	180.0	−120.0	5.4	2.7	1.9
C (14-helix)	7.1	−154.7	64.3	−135.9	4.8	1.7	0.6
D (12-helix)	6.6	−90.0	89.0	−110.0	6.0	3.6	2.8

[a] MP2/6-31G** values. [b] MP2/6-31G** values with solvent effect correction.

and **5**) are quite parallel. That is, **5b** is more favorable than **5c** enthapically by 1.5 kcal/mol but is less favorable than **5c** entropically by 3.9 eu. Thus, in chloroform solvent, **5b** and **5c** are predicted to have similar free energies.

How can our calculations be compared with recent experiments with compound **5**? [19] Both IR and NMR spectra indicate no significant population of intra- and intermolecular hydrogen-bonded conformations for compound **5** in chloroform. While Gellman et al. inferred an extended conformation, our calculations suggest that **5** should mainly exist in the C6 conformation (**5a**) and both C8 and extended conformations have little population. We argue that the C6 conformer is not in disagreement with the experiments because the very weak hydrogen bond should have little influence on the C-terminal N−H stretching and NMR chemical shift of the hydrogen.

Thus, we predict that compounds **4** and **5** both have a preference for a perpendicular dihedral angle ϕ. Compound **5** allows a most stable C6 conformation, but the C6 conformer cannot be allowed for compound **4**.

As a comparison, conformational searches with MACROMODEL (V6.0)[34] using MM2*,[35a] MM3*,[35b] AMBER*,[35c] AMBER94*,[35d] MMFF,[35e] and OPLS*[35f] molecular mechanics force fields were also carried out. The results are summarized in Table 2 of the Supporting Information. In general, conformers **5a**−**d** can be located by these force fields. Several other conformational minima are also generated. But these minima are not stable at the ab initio level and are converted to conformers **5a**−**d** upon geometry optimization. Conformer **5a** is most stable only with the MM2* and MM3* force fields, while conformer **5d** is predicted to be most stable with the other force fields. The variation of the molecular mechanics results from the ab initio results reflects the weakness of these force fields in handling intramolecular electrostatic interaction and hydrogen bonding.[36]

Dipeptide Model 6. When the α-methyl group is introduced, many conformers can be derived from conformers **5a**−**e** and their images. Here, a thorough search for conformational minima was not attempted, but conformational minima that are significant for the secondary structure are believed to be located. For compounds **6**, eight conformational minima are shown in Figure 3 and the calculated ϕ, μ, and ψ and energies are given in Table 1.

Conformers **6a** and **6b**, both in a C6 structure, are derived from **5a** and the image of **5a**, respectively. These two conformers have very similar enthalpies both in the gas phase and in solution. They also have similar entropies. Conformers **6c** and **6d** are derived from conformer **5b** and the image of **5b**, respectively. Conformer **6c** is more stable than **6d** by about 1 kcal/mol because the methyl is anti to the C−NH in **6c** while it is gauche in **6d**. Conformers **6e**,**f** are derived from conformer **5c**. Overall, conformers **6a**−**f** reflect the relative stabilities of unsubstituted conformers **5a**−**c**. Conformer **6g** is derived from conformer **5e**. With the introduction of the α-methyl group to conformer **5f**, both ϕ and ψ rotate so that conformer **6h** is derived. This conformer has its two carbonyl groups nearly parallel. As will be discussed latter, it corresponds to the conformation for the formation of the 12-helix structure. This conformer has a large dipole moment of 6.8 D. It is quite unstable in the gas phase but is significantly stabilized by solvation.

Dipeptide Model 7. Figure 4 shows 10 conformational minima located for compound **7**. Conformers **7a**,**b** are classified as C6. Both of them have reasonably good hydrogen-bond distances. Conformer **7a** is more stable than **7b** both in the gas phase and in solution by over 1 kcal/mol. Conformer **7c** is derived from conformer **5b**. The β-methyl group does not introduce much steric interaction because the methyl is anti to the C_{sp^2}−C bond. We predict that **7c** is only about 0.5 kcal/mol less stable than **7a** both in the gas phase and in solution. Conformers **7d, 7e,** and 7**f** are quite similar. **7e** and **7f** are mirror images if the methyl is not attached. Conformers **7e** and **7f** can be interconverted by the rotation of the dihedral angle ψ by about 50°. Conformers **7g** and **7h** have extended backbones; they are derived from conformer **5c** and its image, respectively. Conformer **7i** is derived from **5e**. It is predicted to be quite high in energy.

Conformer **7j** is most interesting. It corresponds to the local structure for the formation of the 14-helix. It is 4.5 kcal/mol less stable than **7a** in the gas phase, apparently due to the large electrostatic repulsion between the two nearly parallel carbonyl groups. However, it is significantly stabilized by the polar solvent effect. We predict that it might be the most stable conformation in very polar solvent. Even in CH_2Cl_2, we predict that it is only about 0.8 kcal/mol less stable than **7a**.

Secondary Structure of β-Peptides. So far, β-sheets, 14-helices, and 12-helices have been observed for β-peptides.[1−3] We attempt to qualitatively evaluate the tendency of secondary structure formation for unsubstituted, all-α-substituted, and all-

(33) A conformation similar to that of **5b** has been found to be an unusually stable structure when the β-CH_2 is replaced by O: Yang, D.; Ng, F.-F.; Li, Z.-J.; Wu, Y.-D.; Chan, K. W. K.; Wang, D.-P. *J. Am. Chem. Soc.* **1996**, *118*, 9794.

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(36) (a) Smith, D. A.; Vigayakumar, S. *Tetrahedron Lett.* **1991**, *32*, 3613. (b) Gellman, S. H.; Dado, G. P. *Tetrahedron Lett.* **1991**, *32*, 7377. (c) McDonald, D. Q.; Still, W. C. *Tetrahedron Lett.* **1992**, *33*, 7747.

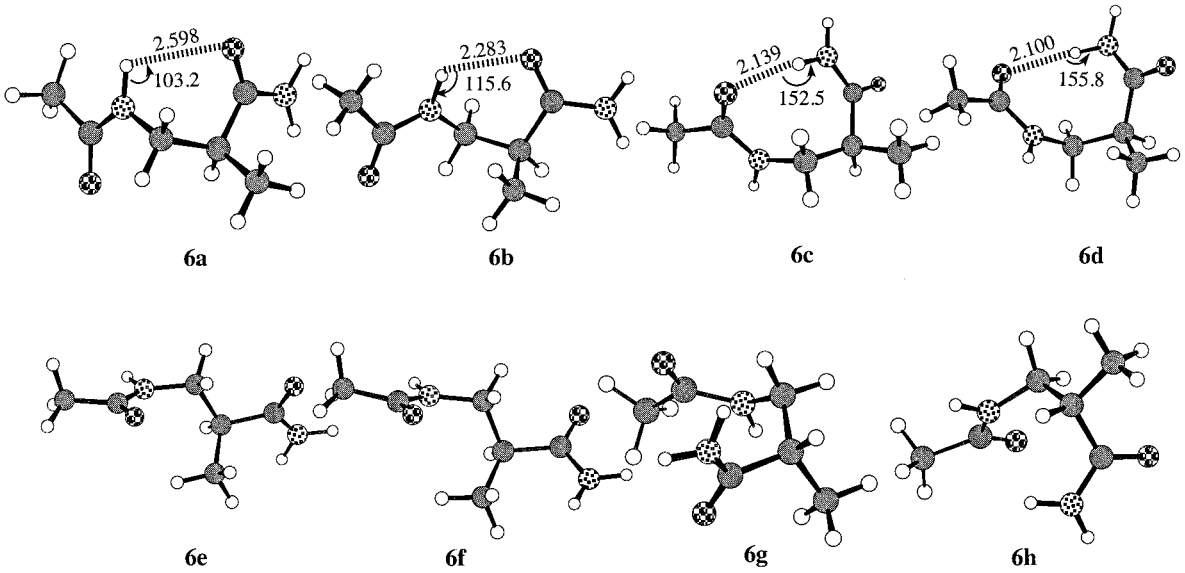


Figure 3. HF/6-31G**-optimized conformers of (*S*)-β-dipeptide model **6**: **6a**, $C6_{eq}$ conformer; **6b**, $C6_{ax}$ conformer; **6c**, $C8_{eq}$ conformer; **6d**, $C8_{ax}$ conformer; **6e**,**f**, extended conformers; **6g**, conformer derived from **5e**; **6h**, conformer for the 12-helix.

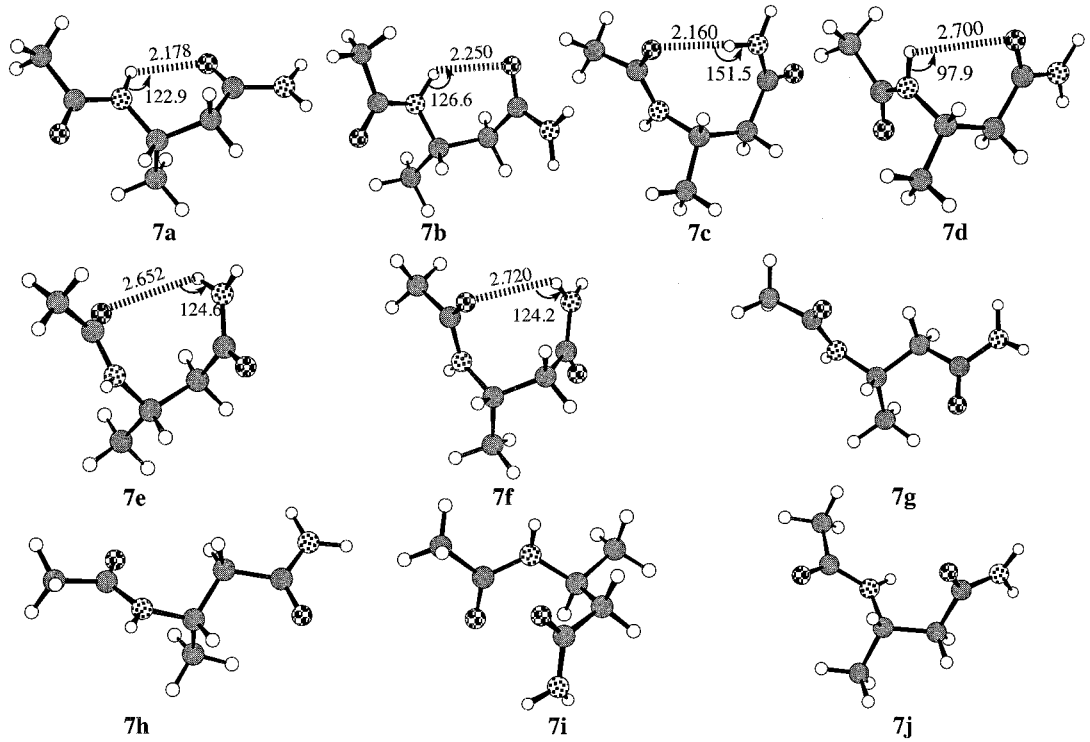


Figure 4. HF/6-31G**-optimized conformers of (*S*)-β-dipeptide model **7**: **7a**,**b**,**d**, C6 conformers; **7c**,**e**,**f**, C8 conformers; **7g**,**h**, extended conformers; **7i**, conformer derived from **5e**; **7j**, conformer for the 14-helix.

β-substituted β-peptides. We note that β-sheet, 14-helix, and 12-helix would have repetitive unique local structures. Thus, dipeptide models **5**−**7** would be suitable for the evaluation of relative preferences of the local structures. This can be achieved by comparing the relative energies of conformers for β-sheet, 14-helix, and 12-helix with the most stable conformer, which is predicted to be the C6 conformation for all three dipeptide models.

The classical β-sheets for α-peptides were originally proposed to be planar and flat. But most of those observed in natural proteins have a right-handed twist, with slightly more positive values of ϕ and ψ.[37] This is believed to result from the intrinsic tendencies of the polypeptide backbone and from its interactions with the side chains. Consequently, the tendency to twist may depend on what amino acid residues are present. In the case of a β-peptide, we used two kinds of local structure models to study the β-sheet. The first is an all-anti conformation with the ϕ, μ, and ψ dihedral angles of 180° (**B**, in Figure 5). This structure is observed in the crystal structure of acetyl-(glycyl-β-alanyl)$_2$-NH-propyl polyamides.[12c] This conformer for dipeptide model **5** is a local minimum in molecular mechanics calculation. However, it is not stable at the HF/6-31G** level and the dihedral angle ϕ rotates to −76° upon optimization (see **5c**). The second one has the three dihedral angles ϕ, μ, and ψ equal to 120°, 180°, and −120°, respectively. This local structure was observed in a previous experiment.[3a] These angles are also

(37) Creighton, T. E. *Proteins: Structure and Molecular Properties*, 2nd ed.; Freeman: New York, 1993; p 182.

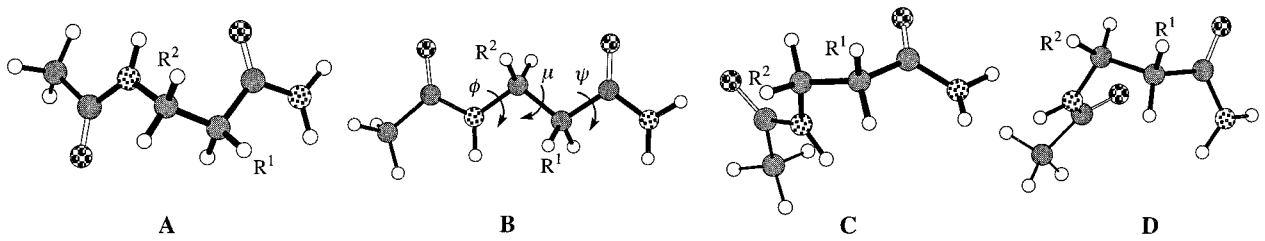


Figure 5. Most stable conformer (**A**) and the conformers leading to β-sheet (**B**), 14-helix (**C**), and 12-helix (**D**) of β-peptide models **5**−**7**.

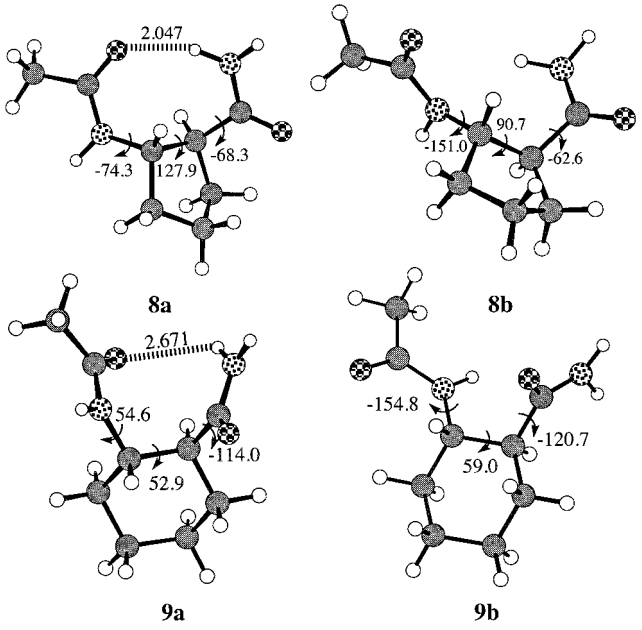


Figure 6. HF/6-31G**-optimized global minima and helical conformers of dipeptide models **8** and **9**.

found in an α,β-dimethyl-β-dipeptide model by the HF/6-31G** calculation,[38] as well as in a three-layer β-sheet model of **6** by AM1 calculations.

For the 14-helix model, we notice that a stable local conformation (**7j**) for compound **7** can be located. The three dihedral angles (−154.7°, 64.3°, −135.9°) in this conformation are close to those in the crystal structure of **3** reported by Gellman et al., which are −136.8°, 56.9°, and −123.3°,[2b] and even closer to those in the 14-helix structures of β-hexapeptide models **10** and **11** calculated with the HF/6-31G* method, as shown in Figure 7. Therefore, these dihedral angels were also applied to **5** and **6**. For the 12-helix model, we were also able to locate a stable conformer (**6h**) for **6**. However, the three dihedral angles are −117.4°, 73.6°, and −85.5°, which are somewhat different from the corresponding values of −90°, 89°, and −110° found in the 12-helix models derived from **10** and **11** (Figure 7). Therefore, the latter values were used for the 12-helix model of **5**−**7**.

The structures for the C6 (**A**), β-sheet (**B**), 14-helix (**C**), and 12-helix (**D**) for dipeptide model **5** are shown in Figure 5. The corresponding structures for dipeptide models **6** and **7** can be derived from methyl substitution at R_1 and R_2, respectively.[39] Table 2 summarizes the calculation results:[40] (1) In the gas phase, **B**−**D** are much higher in energy than **A**, due mainly to the polar repulsion between the two carbonyl groups, as indicated by large dipole moments. (2) Solvation significantly stabilizes conformations **B**−**D** with respect to **A**. The order of solvent effect is roughly 14-helix (**C**) > β-sheet (**B**) > 12-helix (**D**) ≫ C6 (**A**). Solvents with larger dielectric constants ϵ have larger solvent effects. (3) For β-peptides without substituent, the β-sheet can adopt an all-anti conformation. However, for β-peptides with either a α- or β-substituent, the all-anti conformation is considerably destabilized by the steric interaction involving the methyl substituent, and therefore, distortion of the backbone is required to form a β-sheet. (4) In both solvents ($\epsilon = 8.0$, $\epsilon = 33.0$), **C** is more stable than **B**, while **D** is least stable. This is largely due to the smaller solvent effect for **D**. (5) While the α-methyl substituent stabilizes **B**−**D** with respect to **A** (compare **6** with **5**), the β-methyl substituent only has a considerable stabilization for **C** (compare **7** with **5**).

These results allow us to make generalizations and connections with experimental observations: (1) Polar solvents promote the formation of β-sheet and helices. (2) In general, the formation of 14-helix should be more favorable than the formation of 12-helix for β^2-peptides and β^3-peptides (with "natural" side chains in the α- or β-position). The 12-helix should be unfavorable except for some special cases (vide infra). (3) The β^3-peptides should have a stronger tendency to form 14-helix than the β^2-peptides. This is in agreement with Seebach's observation that β^2-peptides have a less stable secondary structure than β^3-peptides, as indicated by their CD spectra.[3f]

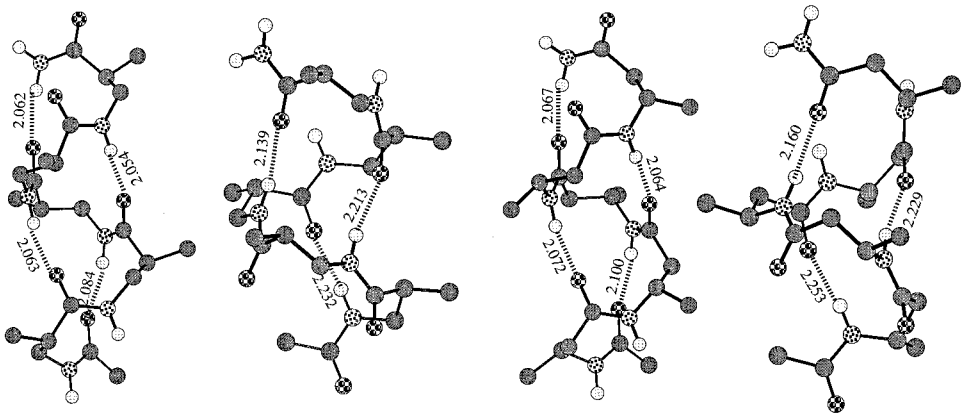
One key difference between the 14-helix and the 12-helix is the dihedral angle about the $C_\alpha-C_\beta$ bond (μ). The former requires the dihedral angle to be about 60°, while the latter, about 90°. To better understand the ready formation of the 12-helix for **2** and the 14-helix for **3**,[2a,b] the conformational preferences of dipeptide models **8** and **9** were studied. The most stable conformation for **8** is a C8 structure (**8a**). This structure is very similar to structure **5d**, with eclipsing about the $C_\alpha-C_\beta$ bond. Conformer **8b** corresponds to the local structure for the formation of the 12-helix. The dihedral angle μ is about 91°. The flatness of the cyclopentane ring does not allow a perfect gauche conformation about the $C_\alpha-C_\beta$ bond. Structure **8b** is only about 1.5 kcal/mol less stable than **8a** by solvation model calculation ($\epsilon = 33.0$). It indicates that the 12-helix can be readily formed if it allows for four or more 12-membered-ring hydrogen bonds which could cause enough stabilization to overcome the preference of **8a** over **8b**.

For compound **9**, the cyclohexane ring restricts the diheral angle μ to about 60°. Quite different from the situations for dipeptide models **5**−**7**, conformer **9a**, which corresponds to structures **7e** and **7f**, is predicted to be most stable in the gas phase. Conformer **9b**, which corresponds to the local structure for the formation of the 14-helix, is predicted to be less stable by 3.2 kcal/mol in the gas phase. However, upon solvation model calculation, **9b** is predicted to be the global minimum in a proper polar solvent. This means that each residue in **2** exists in a most favorable conformation that is ideal for the formation of the 14-helix.

(38) Wu, Y.-D.; Wang D.-P. Unpublished results.

(39) The **A** for dipeptide model **7** shown in Figure 5 is the mirror image of **7a** in Figure 4.

(40) Except for **A** and **C** for **7**, the structures are not conformational minima. Therefore, thermal energy and entropy are not included.



	10a	**10b**	**11a**	**11b**
ΔE(gas):	0.0	6.5	0.0	2.7
ΔE(sol., ε=33.0):	0.0	2.0	2.5	0.0
ΔE(sol., ε=8.0):	0.0	1.3	1.3	0.0
(ϕ,μ,ψ) average:	(-90.3, 88.9, -109.1)	(-146.7, 58.5, -131.5)	(-88.5, 89.3, -111.4)	(-145.5, 60.3, -135.9)

Figure 7. HF/6-31G*-optimized 12-helix (**10a**, **11a**) and 14-helix (**10b**, **11b**) β-hexapeptide models **10** and **11**. All of the hydrogens bonded to carbon atoms are omitted. The relative energies (kcal/mol) are calculated at the B3LYP/6-31G* level using HF/6-31G*-optimized structures. The (ϕ, μ, ψ) are the average dihedral angles of the helices. The calculated dipole moments of **10a**, **10b**, **11a**, and **11b** are 21.2, 22.9, 21.5, and 22.4 D, respectively.

To better understand the structure and the tendency for the formation of the 14-helix and 12-helix, we fully optimized the β-hexapeptide models **10** and **11**. The 12-helices (**10a**, **11a**) form four hydrogen bonds, while the 14-helices (**10b**, **11b**) allow for only three hydrogen bonds. In addition, the O- - -H hydrogen-bond lengths in **10a** and **11a** are shorter than 2.1 Å, while those in **10b** and **11b** range from 2.14 to 2.25 Å, indicating stronger hydrogen bonds for the 12-helix. The hydrogen bond involving the N-terminal N−H in each structure is the weakest according to the O- - -H−N distance. The 12-helices, which are thinner, have a pitch of about 5.7 Å, and each turn contains about 2.5 residues. The 14-helices, have a pitch of about 5.1 Å with about 3 residues per turn. These are quite close to the X-ray crystal structures of **2** and **3**.[2a,b] Energetically, the B3LYP/6-31G* calculations give 6.5 and 2.7 kcal/mol preference to **10a** and **11a** over **10b** and **11b**, respectively, in the gas phase. Two points can be noticed: (1) Even in the gas phase, a β^3-peptide has a stronger tendency for the 14-helix formation than a β^2-peptide. (2) If the extra hydrogen bond in **10a** and **11a** causes about 4−5 kcal/mol stabilization, we can qualitatively conclude that when the possible number of hydrogen bonds is the same for the 12-helix and 14-helix, which is the case for most experiments, β^2-peptides should have a somewhat greater tendency to form a 12-helix, probably due to stronger hydrogen bonding. This is in accord with the gas-phase energy difference between **C** and **D** shown in Table 2. That is, **C** and **D** have similar stabilities for **6**, but **C** is more stable than **D** for **7** by 1.2 kcal/mol.

Just as in the dipeptide models **5**−**7**, where the conformation **C** for the 14-helix is more stabilized than the conformation **D** for the 12-helix by solvation, the 14-helical structures **10b** and **11b** are also more stabilized than the 12-helical structures **10a** and **11a** by solvation. Interestingly, for hexapeptide model **10**, the 12-helix is predicted to be still somewhat more stable than the 14-helix, while the 14-helix is more stable than the 12-helix for **11**. It should be noted that these predictions are only of qualitative value. This is because (1) entropy differences are not calculated and (2) the solvation model calculations may give different solvent effects with different isodensity values. Nevertheless, the promotion of 14-helix formation by alkyl substituents at the β-position is clearly indicated by the calculations.

Recently, Seebach et al. observed a new kind of helical structure with a 12/10/12 sequence for the hydrogen-bond pattern in "mixed" β-peptides.[4] The repeating unit of this kind of helix involves two residues with different sets of ϕ, μ, and ψ dihedral angles. One of the local structures corresponds to conformers **6g** and **7i**; the other corresponds to conformers **7e** and **7f**. Although our current calculations indicate that such a helical structure should be accessible, it is difficult for us to make a comparison between this and the formation of the 14-helix and 12-helix with the current calculation. Such a comparison would require calculations for β-peptide models with at least three residues, and work in this line is currently being carried out.[41]

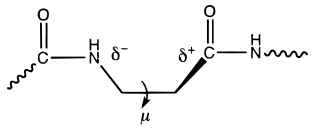
Higher Helical Propensity of β-Peptide than α-Peptide. Previous calculations on alanine dipeptide model, (*S*)-2-(acetylamino)-*N*-methylpropanamide, indicated that in the gas phase there is no conformational minimum in the regions of ϕ and ψ space corresponding to protein secondary structures.[17] The solvation calculation using the Onsager model indicated that the conformation corresponding to α-helix can be located in water.[17b] But this conformation is still about 1.6 kcal/mol less stable than the most stable $C7_{eq}$ conformer at the HF/3-21G level.

The current calculations reveal that β-peptide models **5**−**7** can exist in many folded conformational minima, each with a gauche μ dihedral angle. Some folded conformations (**5e**,**f**, **6g**,**h**, **7e**,**f**,**i**,**j**) correspond to the formation of helical structures. In particular, the conformation that corresponds to the 14-helix is most stable for dipeptide models **7** and **9** (**7j**, **9b**) in polar solvents. This is in good agreement with the experimental observation that β^3-peptides and peptides **3** can easily form the 14-helix.

What is the cause of the folded structures for β-peptides? We argue that there are favorable internal non-hydrogen-bonded electrostatic (or dipole) interactions for these structures. In particular, there is a preference for the μ dihedral angle to be gauche instead of anti. As shown in **12**, the negatively charged N has an attractive interaction with the positively charged

(41) Preliminary calculations indicate that the formation of the 12/10/12 helix is favorable for certain paterns of substitutions. Wu, Y.- D.; Wang D.-P. Unpublished results.

carbonyl carbon in the gauche conformation. Such internal electrostatic interactions might play important roles in many biological systems.[42]



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Summary

We have theoretically studied the conformational features of β-peptide models **4**−**9** and β-hexapeptide models **10**−**11**. The results can be summarized as follows: (1) The current calculations give results in agreement with experimental observations for dipeptide model **4**. (2) For dipeptide model **5**, we predict that the most stable conformation is in a C6 structure with essentially no hydrogen bonding. We believe that this is also in accord with experimental observation of no intramolecular hydrogen bonding for compound **5**.[17] In addition, the C6 structure is the most stable conformer for **6** and **7** as well. (3) The local conformations for β-sheet, 14-helix, and 12-helix are highly unstable in the gas phase but are significantly stabilized by polar solvent effect. The solvent effect is in the order 14-helix > β-sheet > 12-helix ≫ C6. (4) The 14-helix is intrinsically more favorable than the 12-helix. This preference is increased by β-substituents but reduced by α-substituents. (5) The five-membered ring and six-membered ring in models **8** and **9** can promote the formation of 12-helix and 14-helix, respectively. (6) For β^2-peptides similar to **10**, the formation of the 12-helix is predicted to be more favorable.

Acknowledgment. We thank Professor Dan Yang (The University of Hong Kong) for helpful discussions and Professor D. Seebach (ETH-Zentrum) for sending us preprints of related papers. We are grateful to the University Grants Council of Hong Kong for financial support of the work.

Supporting Information Available: Tables of calculated energies, thermal energies of conformers for dipeptide models **5**−**9**, and molecular mechanics calculation results on dipeptide model **5** (4 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

JA981939B

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