Theoretical Study of Peptides Formed by Aminoxy Acids

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Abstract: Quantum mechanics methods have been applied to study the conformational features of peptides formed by aminoxy acids. Geometry and vibration frequencies were calculated by the HF/6-31G** method. Energy was further evaluated using the MP2/6-31G** or B3LYP/6-31G* calculation. Solvent effect was modeled by the self-consistent isosurface polarization continuum model with the HF/6-31G** method. There is a significant preference for the formation of an eight-membered-ring hydrogen bond between adjacent amino acid residues, which resembles a γ-turn. The rotation direction of the C8 structure is determined by the chirality of the Cα center and is independent upon the size of the alkyl side chain. There is a cooperative effect for the formation of adjacent C8 structures, which promotes the formation of helix. Thus, a homo (*S*)-oxa-polypeptide forms a right-handed 1.8_8-helix, with each turn of the helix containing about 1.8 units of aminoxy acids.

Introduction

One of the challenging issues in molecular design is the control of three-dimensional structures.[1] There is tremendous current interest in developing peptidomimetics with unnatural amino acids to form controllable secondary structures (foldmers).[2−9] Natural peptides or proteins most frequently form α-helix, β-sheet structures, as well as β-turns (**A**).[10] The formation of α-helix usually requires more than 15 residues.[11] On the other hand, β-peptides, peptides of β-amino acids, can form 14-helix, 12-helix (**B**), and 10/12-mixed helix (**C**), with relatively short peptides (4−6 residues).[2−5] Turns and sheet structures have also been reported for β-peptides.[12−13] γ-Peptides, which consist of entirely γ-amino acids, can also easily form helical structures.[6]

Oxa-peptides, peptides of α-aminoxy acids, are analogues of β-peptides, with the C_β replaced by O. It has been found that homochiral oxa-peptides form 1.8_8-helix (**D**), which features a stable 8-membered-ring hydrogen bond between each adjacent pair of residues.[9] While the chemistry of β-peptides and oxa-peptides is still evolving, an understanding of the conformational features of these peptides from a theoretical point of view is important for the design of peptides with new scafold.[14,15] In this paper, we report a detailed theoretical study to illustrate the conformational features of oxa-peptides. Scheme 2 gives the molecular systems that have been studied.

Method of Computation

All calculations were carried out with the GAUSSIAN 94 program.[16] For models **1**−**6**, geometries were fully optimized by the HF/6-31G**

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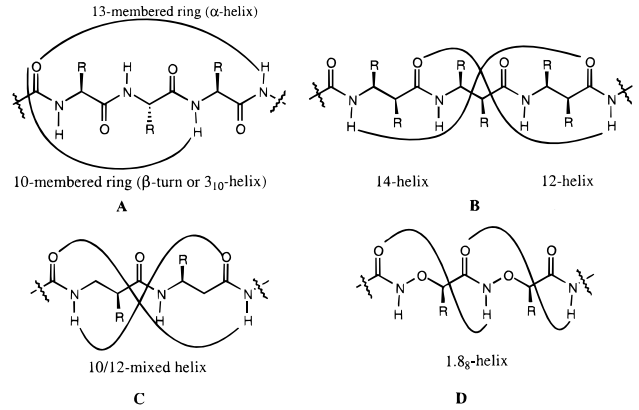
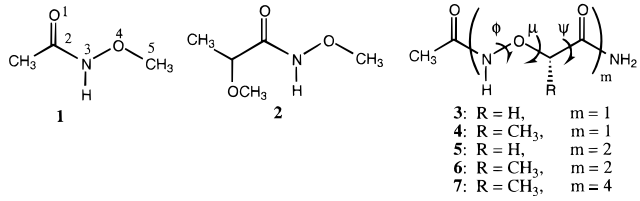
Scheme 1



Scheme 2



method. Energies were evaluated using the MP2/6-31G** calculations on the HF/6-31G** geometries. For compounds **1**−**4**, harmonic vibration frequency calculations were also carried out with the HF/6-31G** method. Solvent should have a large effect on the conformational stability, and is modeled by the SCIPCM method[17,18] at the HF/6-31G** level. An isodensity value of 0.0008 was used for all the calculations, which has been shown to give good results for β-peptides.[14] A dielectric constant of 4.1 was set to model the $CHCl_3$ solvent. The relative energies of conformers were further calculated with the MP2/6-31G** energies plus the solvation energy correction. Relative free energies were calculated with the thermal energy and entropy corrections. For compound **7**, geometry optimization was carried out with the HF/6-31G* method and energy evaluation with the density functional theory B3LYP/6-31G* method.[19]

Results and Discussion

Methoxyamides 1 and 2. Our first step is to study the conformational features about the amide C−N and N−O bonds. Two models were employed. Model **1** is for the terminal amide situation and model **2** is for the internal environment. In the gas phase, the (*Z*)-structure **1a** is less stable than the (*E*)-structure **1b** by 1.6 kcal/mol for **1**. A similar result was obtained by Turi et al. for *N*-hydroxyacetamide.[20] This is expected because of an electrostatic repulsion between the two oxygen atoms in **1a**. In $CHCl_3$ solvent, the (*E*)-preference is reduced to 0.8 kcal/mol. With entropy consideration, the free energy of the (*Z*)-structure is calculated to be only 0.4 kcal/mol higher than that of the (*E*)-structure.

For model **2**, the α-methoxy group is anti to the carbonyl C═O bond, so that the C−O/C−O dipole interaction is most favorable. As will be seen later, this is the favored conformation in oxa-peptides.[21] Contrary to model **1**, the conformation for the (*Z*)-structure (**2a**) is more stable than that for the (*E*)-structure (**2b**) by 2.0 kcal/mol in the gas phase and 2.8 kcal/mol in $CHCl_3$ solution. The reversal in the stability of (*E*)- and (*Z*)-structures is due to the large repulsive interaction between the two methoxy oxygen atoms in the (*E*)-structure **2b**. The O/O distance is only 2.8 Å. Thus, the conformational preference is the same for the internal alkoxy amide bond as for the normal amide bond.[22]

One significant geometrical feature of the alkoxy amides is the considerable pyramidalization at the amide nitrogen atom. The O═C−N−O and O═C−N−H dihedral angles are 21° and 154°, respectively. This pyramidalization is induced by the vicinal lone-pair/lone-pair interaction about the N−O bond, so that electrostatic repulsion is reduced. The pyramidalization is much smaller for normal amides.[23]

The barrier of normal amide C−N bond rotation has been studied extensively,[24] due to the importance of proline isomerization in protein folding and the findings that certain immunosuppressive agents such as cyclosporin A, FK506, and rapamycin bind to peptidyl-prolyl isomerases.[25] In the case of dimethylacetamide (DMA), the calculated $\Delta G^{\ddagger}$ is about 15−16 kcal/mol in the gas phase.[24] It increases with increasing solvent polarity and becomes about 19 kcal/mol in water.[24a] The anti (**1c**) and syn (**1d**) transition structures for the C−N bond rotation of **1** are shown in Figure 2,[26] anti and syn referring the orientation of the nitrogen lone pair with the C═O bond. In both transition structures the methoxyl group is syn to the nitrogen lone pair.[27] Three distinctions can be found with respect to normal amide. (1) The calculated barrier of C−N bond rotation in the gas phase is somewhat lower than that of normal amide. This can be attributed to the pyramidalization of the nitrogen atom in **1a** and **1b**. The pyramidalization reduces conjugation in oxa-amides, as indicated by the longer amide C−N bonds in **1a** and **1b** (also **2**) than those in normal amides. (2) There is little solvent effect on the barrier of rotation. This is probably due to similar dipole moments for the ground state and the transition structure (see Table 1). (3) the syn transition structure (**1d**) is slightly more stable than the anti transition structure (**1c**), while for DMA the syn transition structure is about 3−4 kcal/mol less stable than the anti transition structure.[24]

As expected, the N−O bond is quite rigid. In structures **1b** and **2b**, the C2−N3−O4−C5 dihedral angle (for atom numbering, see **1** in Scheme 2) is about perpendicular to minimize the

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(27) Another anti transition structure was also located. It has the nitrogen lone pair nearly antiperiplanar to the O4−C5 bond, and is less stable than **1c** and **1d** by about 2−3 kcal/mol.

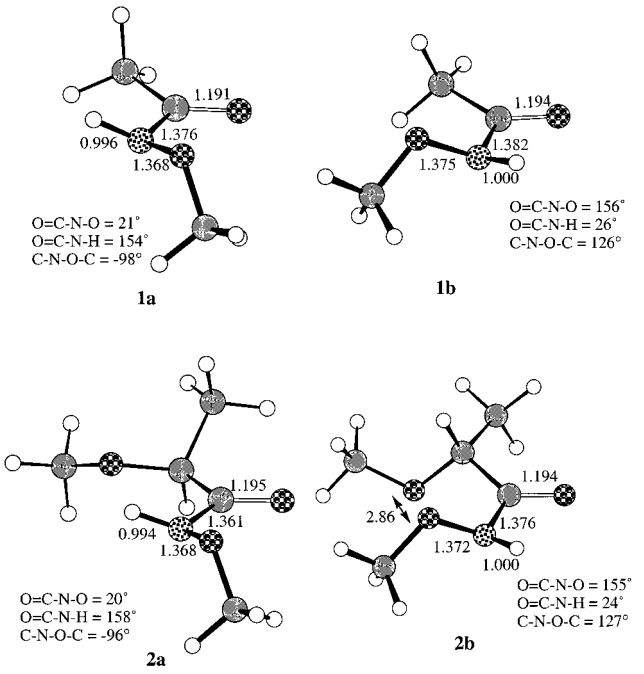

Figure 1. HF/6-31G** optimized (*Z*)- and (*E*)-conformers of *N*-methoxyamides **1** and **2**.

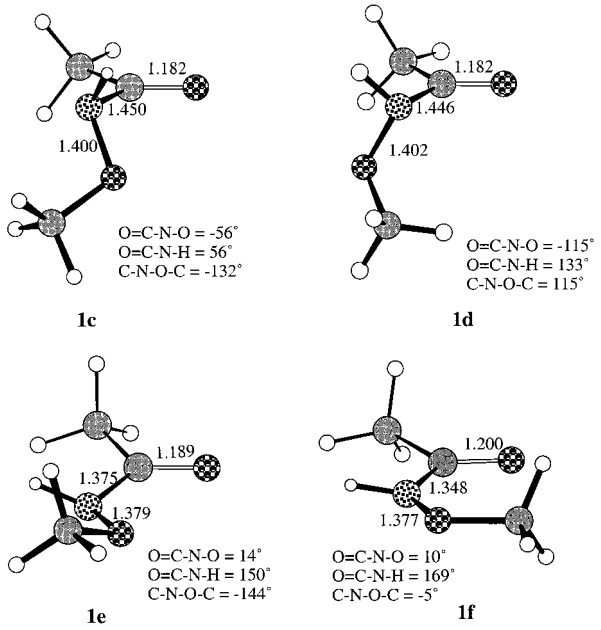

Figure 2. HF/6-31G** optimized rotational transition states about C−N (**1c** and **1d**) and N−O (**1e** and **1f**) bonds of *N*-methoxyacetamide **1**.

lone-pair/lone-pair repulsion.[28] Two transition structures for the N3−O4 bond rotation of model **1** have been located, with **1e** for outward rotation, and **1f** for inward rotation. Both transition structures have eclipsed conformation about the N3−O4 bond. In **1e**, the H−N3−O4−C5 dihedral angle is about 7°, while in **1f**, the C2−N3−O4−C5 dihedral angle (ϕ) is about −5°. The calculated barrier to rotation is 6.8 and 9.8 kcal/mol with **1e** and **1f**, respectively. These high barriers are mainly due to lone-pair/lone-pair repulsions in **1e** and **1f**.[29] Structure **1f** is higher in energy than **1e** due to a severe steric interaction between the eclipsing methyl group and the carbonyl group.

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Table 1. Calculated Dipole Moments, Thermal Energies, Torsional Angles, Entropies, Relative Enthalpies in the Gas Phase, and Relative Enthalpies and Free Energies (298 K) in Solution for the Conformational Stationary Points of *N*-methoxyamides **1** and **2**[a]

	gas phase						solv. SCIPCM model	
conf.	dipole (D)	$E_{(thermal)}$	ω	ϕ	S[b]	ΔH[c]	ΔH[d]	ΔG[e]
				monopeptide model **1**				
1a	3.5	76.1	−161.3	−97.5	82.5	1.6	0.8	0.4
1b	3.6	76.1	26.0	−125.7	81.2	0.0	0.0	0.0
1c	3.2	75.2	125.0	−132.4	79.3	14.3	14.3	14.9
1d	2.7	75.4	64.5	114.9	79.1	13.6	12.7	13.3
1e	5.2	75.2	−168.3	144.3	80.1	8.6	6.1	6.8
1f	2.6	75.5	−172.0	−4.8	80.2	9.5	9.3	9.6
				monopeptide model **2**				
2a	4.0	119.8	139.4	−95.9	101.5	0.0	0.0	0.0
2b	3.7	119.8	174.4	−126.9	99.0	2.0	2.3	3.0

[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.

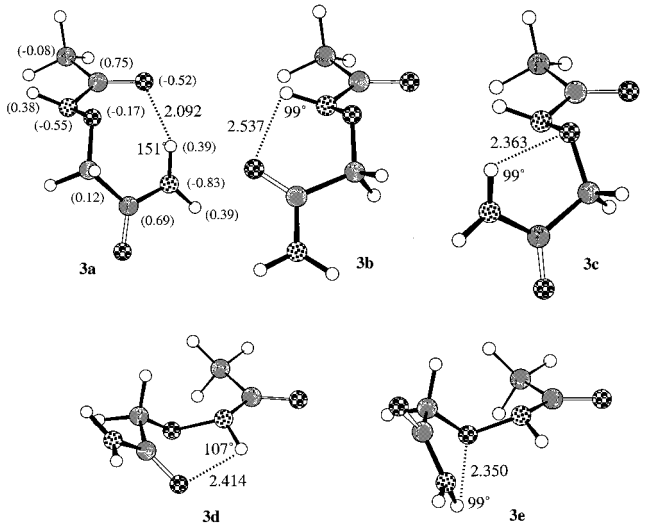

Figure 3. HF/6-31G** optimized conformers of oxa-dipeptide model **3**. The values in parentheses for **3a** are MSK atomic charges[27] (hydrogens are summed into carbon atoms) with the B3LYP/6-31G** method.

Dipeptide Models 3 and 4. Figure 3 shows the five conformational minima found for dipeptide model **3**. Structure **3a** is in an 8-m-r hydrogen-bonded conformation, referred to as C8 conformation. There is a good hydrogen bond in **3a**, as indicated by the O- - -H distance of 2.1 Å and N−H- - -O angle of 151°. The dihedral angle ϕ is about 127°, somewhat deviate from the ideal perpendicular position. Structures **3b** and **3d** are formally in the 6-m-r conformation, referred to as C6 conformation. However, the hydrogen bond is weak, as indicated by the long O- - -H distance and small N−H- - -O angle. Structures **3c** and **3e**, which differ from **3b** and **3d** in the dihedral angle ψ, have even weaker hydrogen bonds, as the oxa oxygen is much less negatively charged than the carbonyl oxygen. Calculations indicate that **3a** is over 2 kcal/mol more stable than structures **3b**−**d** in both the gas phase and $CHCl_3$ solution.

Interestingly, each structure has a gauche N−O−C−C dihedral angle (μ). We were unable to locate a stable minimum with an anti N−O−C−C dihedral angle. We propose that there

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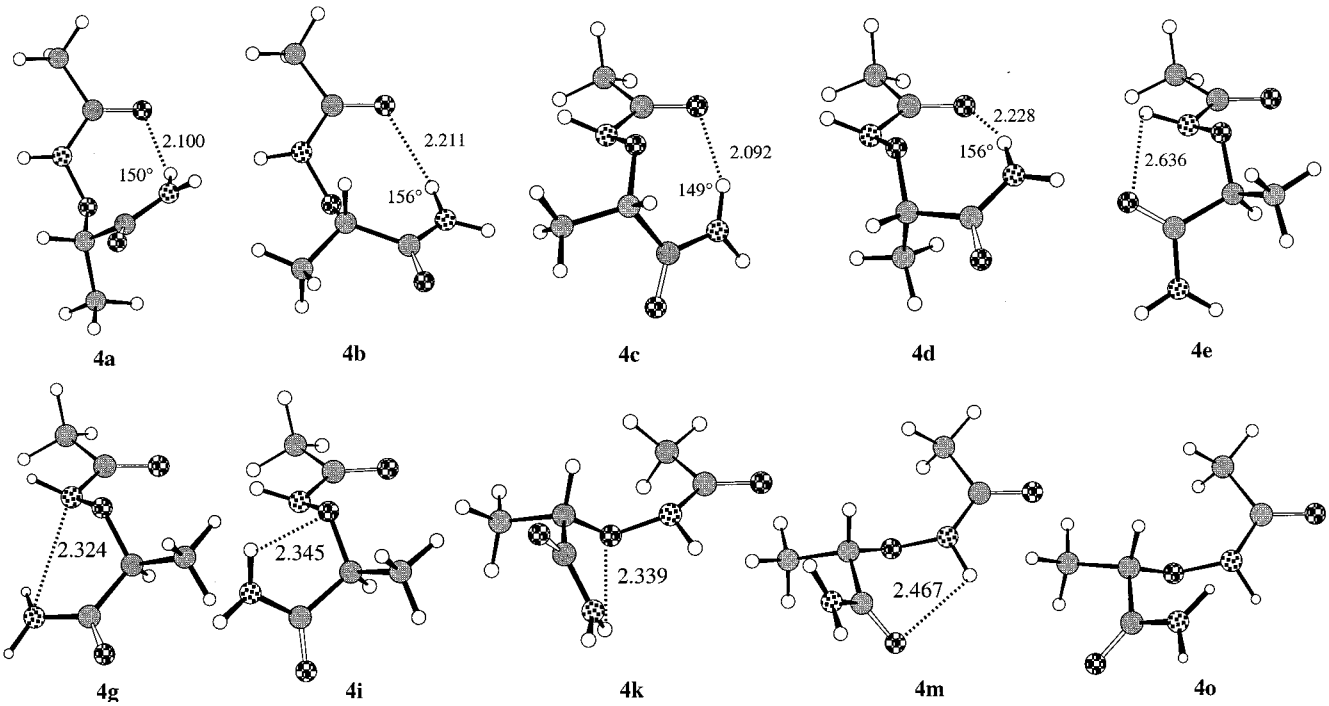
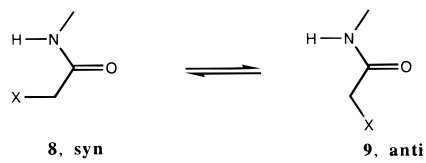


Figure 4. HF/6-31G** optimized conformers of oxa-dipeptide model **4**.

is an intrinsic electrostatic stabilization for the gauche conformation. As shown in **3a**, the amide nitrogen carries negative charge, and the carbonyl carbon carries positive charge.[30] They are attractive in the gauche conformation. We also found the same gauche preference for β-peptides, where the oxygen atom is replaced by a carbon atom.[14] This feature has been regarded as an important factor for easy formation of helical structures for β-peptides.

The prediction that oxa-dipeptide favors the C8-turn structure has been confirmed by experiments. Oxa-dipeptide models show much weaker amide N−H stretching in IR spectra, and downfield chemical shift in ^{1}H NMR spectra, indicating the formation of an 8-m-r hydrogen bond.[9] In addition, crystal structures of a dipeptide model have also been obtained, which exists in a C8 conformation.[9] However, for an analogous β-dipeptide model experiments indicate that the major population of conformers have no hydrogen bond.[31,32] Our calculations for an unsubstituted dipeptide model suggest that a C6 structure similar to **3d** is more stable than a C8 conformation by 1.9 and 1.2 kcal/mol in the gas phase and in CH_2Cl_2 solution, respectively.[14a]

The dramatic difference in conformational features between β-peptides and oxa-peptides can be mainly attributed to the conformational preference of the N−Csp2−C−X dihedral angle (ψ). In the C8 conformation, it is required that N−Csp2−C−X be syn (**8**, ψ close to 0°), while in the C6 conformation, the



8, **syn**
X = O, favored

9, **anti**
X = C, favored

dihedral angle should be anti (**9**, ψ close to 180°). For β-peptides, the dihedral angle ψ prefers 180° to 0°. Therefore, the C6 conformation is favored. In contrast, for oxa-peptides, the syn conformation is favored. In addition, the electron-withdrawing ability of the *N*-alkoxyl group of the oxa-peptide also promotes hydrogen-bonding interaction, and therefore, favors the C8 conformation. It should be noted that the conformational rigidity about the N−O bond is also a factor for the secondary structure of oxa-peptides (vide infra).

When a methyl group is introduced to the α-carbon center, model **4**, many more conformations become possible. A total of 16 conformers of **4** have been investigated, 10 of which are shown in Figure 4. The calculated relative energies and geometrical information of those conformers are given in Table 2. Other conformers all have the methyl group gauche to the O−N bond, and thus are considerably higher in energy.

Four C8 conformers were obtained by the HF/6-31G** method. The *C*-terminus points forward in conformers **4a** and **4b** and backward in **4c** and **4d**. Conformers **4a** and **4b** differ mainly in the dihedral angle μ, which is about −78° in **4a** and −137° in **4b**. As a result, the methyl group is anti to the N3−O4 bond in **4a** but gauche in **4b**. As expected, **4b** is less stable than **4a** by about 0.7 kcal/mol in $CHCl_3$. Structure **4c** also has the methyl group gauche to the N3−O4 bond. In the gas phase it is only 0.7 kcal/mol less stable than **4a** enthalpically. With entropy and solvent effect correction, it becomes 1.6 kcal/mol less stable than **4a**. In **4d**, the methyl is eclipsed with the N3−O4 bond. This structure is less stable than **4a** by about 3 kcal/mol. Geometry optimization with the density functional theory B3LYP/6-31G** method was also performed for these structures.[33] Only **4a** and **4c** were found to be conformational

(30) Atomic charges were calculated with the Merz−Singh−Kollman potential energy fitting scheme: (a) Besler, B. H.; Merz, K. M.; Kollman, P. A. *J. Comput. Chem.* **1990**, *11*, 431. (b) Singh, U. C.; Kollman, P. A. *J. Comput. Chem.* **1984**, *5*, 129.

(31) (a) Gung, B. W.; MacKay, J. A.; Zou, D. *J. Org. Chem.* **1999**, *64*, 700. (b) Dado, G. P.; Gellman, S. H. *J. Am. Chem. Soc.* **1994**, *116*, 1054. (c) Marraud, M.; Neel, J. *J. Polym. Sci.* **1975**, 271

(32) Our calculations also suggest that a β-methyl substituent of a β-dipeptide model considerably increases the hydrogen bond strength in the C6 structure (ref 14). This is in agreement with recent experimental observation by Gung et al. (see ref 31a).

(33) The density functional calculations were also carried out for other selected structures. Because the geometries and relative energies are very similar to those calculated by the HF2/6-31G** method, these results are not reported in detail here.

Table 2. Calculated Dipole Moments, Thermal Energies, Torsional Angles, Entropies, Relative Enthalpies in the Gas Phase, and Relative Enthalpies and Free Energies (298 K) in Solution for the Conformers of Oxa-Dipeptide Models **3** and **4**[a]

	gas phase							solv. SCIPCM model	
conf.	dipole (D)	ϕ	μ	ψ	$E_{(\text{thermal})}$	S[b]	ΔH^c	ΔH^d	ΔG^e
				dipeptide model **3**					
3a	5.3	127.5	−83.0	−13.0	96.8	96.3	0.0	0.0	0.0
3b	3.7	−116.0	−70.7	−117.8	96.4	100.6	4.8	3.8	2.5
3c	5.4	−101.0	−79.4	−20.0	96.6	98.9	4.3	3.3	2.6
3d	6.9	−136.6	−70.7	−176.2	96.4	98.3	3.3	2.8	2.2
3e	3.7	−128.8	−80.0	−16.5	96.6	97.0	2.5	2.5	2.3
				dipeptide model **4**					
4a	5.6	129.6	−77.7	−19.8	116.4	102.7	0.0	0.0	0.0
4b	6.2	110.0	−136.9	30.2	116.2	103.8	0.7	1.0	0.7
4c	5.4	−130.6	73.3	22.9	116.4	101.5	0.7	1.2	1.6
4d	6.1	−111.4	137.5	−30.2	116.3	103.0	2.7	2.9	2.9
4e	3.4	−110.0	−64.3	165.2	116.0	105.7	4.9	4.0	3.1
4f	4.7	121.9	70.2	168.0	116.0	105.0	5.3	4.7	4.0
4g	6.0	−92.8	−84.2	45.0	116.1	106.0	6.3	5.8	4.8
4h	5.9	111.4	74.6	−48.6	116.2	103.7	7.6	6.9	6.6
4i	5.1	−100.6	−78.9	−21.5	116.1	105.3	3.8	3.1	2.3
4j	4.5	116.8	71.8	25.0	116.2	103.2	4.4	3.8	3.6
4k	4.0	−128.6	−77.0	−19.3	116.1	103.2	2.3	2.2	2.0
4l	3.8	137.3	71.7	22.9	116.2	102.0	3.1	3.4	3.6
4m	6.5	−133.2	−64.3	165.8	116.0	103.7	3.5	3.1	2.8
4n	7.3	−143.2	−71.6	−163.4	116.0	103.3	4.7	4.3	4.1
4o	2.3	−122.6	−75.7	77.7	116.1	104.8	4.6	4.8	4.2
4p	2.31	−132.2	70.7	57.8	116.3	102.7	6.7	7.0	7.0

[a−e] Same as those in Table 1.

minima, and **4b** and **4d** were converted to **4a** and **4c**, respectively. There is no rotational barrier between **4a** and **4b**, and between **4c** and **4d** with the DFT method. Indeed, the barrier for the conversion of **4b** and **4d** to **4a** and **4c**, respectively, with the HF/6-31G** method is also very low, only about 0.2 kcal/mol.

Structures **4e**−**p** can be derived from structures **3c**−**e**. Structures **4e**, **4g**, **4i**, **4k**, **4m**, and **4o** all have the methyl group anti to the N3−O4 bond, which causes little steric interaction. Therefore, the relative energies of these structures with respect to **4a** are similar to those of **3c**−**e** with respect to **3a**, ranging from 2.0 to 3.1 kcal/mol. Structures **4f**, **4h**, **4j**, **4l**, **4n**, and **4p**, which are not shown in Figure 4, can be visualized as the mirror image of structures **4e**, **4g**, **4i**, **4k**, and **4m**, respectively, but with the methyl group at the hydrogen position. Because the methyl group is gauche to the N3−O4 bond, these structures are higher in energy.

In summary, chiral dipeptides are predicted to favor the C8 structure. This local structure resembles a γ-turn, which is found in proteins but itself is not stable.[10,34] There is a strong preference for the turn to be right-handed if the α-carbon is in the (S)-configuration, and to be left-handed if the α-carbon is in the (R)-configuration. This preference is caused by the steric effect of the side chain, which favors to be anti to the N3−O4 bond to avoid steric interaction with the N3−H group. Since the methyl group used in the calculations is the smallest alkyl group, the preference of the turn direction is expected to be even larger if the side chain involves other alkyl groups. In other words, the direction of the turn is not affected by the nature of the side chain.

Tripeptide Models 5 and 6. A conformational search for the tripeptide model **5** indicates that it has much fewer conformational minima than the corresponding β-tripeptide model has. Several low-energy conformers of tripeptide model **5** are shown in Figure 5. The most stable conformtions have two contiguous C8 structures (**5a** and **5b**). Other conformations have either one or no C8 unit, and are much higher in energy (Table 3). Conformer **5a** has the two C8 units turning in the same direction, corresponding to a helical structure. **5b** has the two C8 units in the opposite direction of rotation to form a β-turn-like structure. At each level of calculation, **5a** is more stable than **5b**. A closer look indicates that the O- - -H(N) distances in **5a** are slightly shorter and the O- - -H−N angles are somewhat larger than those in **5b**. Thus, the formation of C8 turn structures is cooperative, which promotes the formation of helix.

For a corresponding β-tripeptide, several low-energy 10-m-r and 12-m-r hydrogen-bonded structures can be located.[14b] They are responsible for the easy formation of secondary structures such as the 12-helix, 10/12-helix, and turn structures.[3b,5] These types of conformations were also explored for model **5**. Starting from a 12-m-r hydrogen-bonded structure corresponding to the 12-helix, geometry optimization leads to structure **5a**. The 10-m-r and 12-m-r structures corresponding to the 10/12-mixed helix lead to structures **5g** and **5h**, respectively. Structure **5c** is also derived from a 12-m-r hydrogen-bonded starting geometry corresponding to a turn. Thus, 10-m-r and 12-m-r hydrogen-bonded structures are highly unstable, and they are converted to structures with either one or two C8 units.

For methyl-substituted (S,S)-tripeptide model **6**, only contiguous C8 conformations were explored. Four structures were located which are shown in Figure 6. Structure **6a** is derived from **5a**, in which both C8 rings adopt the conformation of **4a**. The methyl group has little effect on the backbone geometry as indicated by dihedral angles. Structure **6b** has the *N*-terminus C8 unit in the conformation of **4a** while the *C*-terminus one in the conformation of **4b**. Structure **6c** has both C8 units in the conformation of **4b**. While **4a** is more stable than **4b** by about 0.7 kcal/mol, the preference for **4a** in the tripeptide is somewhat larger. Structure **6d**, derived from **5b**, with the *N*-terminus C8 unit in the conformation of **4c** and the *C*-terminus C8 unit in the conformation of **4a**, is about 1.6 kcal/mol less stable than **6a**. This can be qualitatively explained by the two destabilizing factors in **6d**. (1) The backbones of **6a** and **6b** correspond to **4a** and **4b**, with **4b** being less stable than **4a** by about 0.6 kcal/mol. (2) The *N*-terminus C8 unit of **6d** is in the **4c** conformation, which is about 1.2 kcal/mol less stable than **4a** (see ΔH in Table 2). Therefore, for a homo-(*S*)-oxa-peptide, it is expected that a right-handed helix like **6a** is formed.

Pentapeptide Model 7. To test the above idea, pentapeptide model **7** was studied. A molecular mechanics conformational search was first performed with the Macromodel program[35] using a modified AMBER94* force field.[36] It generated 103 unique conformational minima within 10 kcal/mol. Besides the expected helical structure with four contiguous C8 units, four "cyclic" structures that were lower in energy than the helical structure were also located. Among those "cyclic" structures, the most stable one, which is also the global minimum, retains the four contiguous C8 units but also forms a hydrogen bond between the two termina (see **7b**).

(34) A similar γ-turn structure has been reported by Dupond et al., which involves an eight-membered-ring hydrogen bonding between an amide carbonyl group and the hydroxyl group of *N*-hydroxy amide: Dupont, V.; Lecoq, A.; Mangeot, J.-P.; Aubry, A.; Boussard, G.; Marraud, M. J. *J. Am. Chem. Soc.* **1993**, *115*, 8898.

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(36) Cornell, W. D.; Cieplak, P.; Bayly, C. I.; Gould, I. R.; Merz, K. M.; Ferguson, D. M.; Spellmeyer, D. C.; Fox, T.; Caldwell, J. W.; Kollman, P. A. *J. Am. Chem. Soc.* **1995**, *117*, 5179.

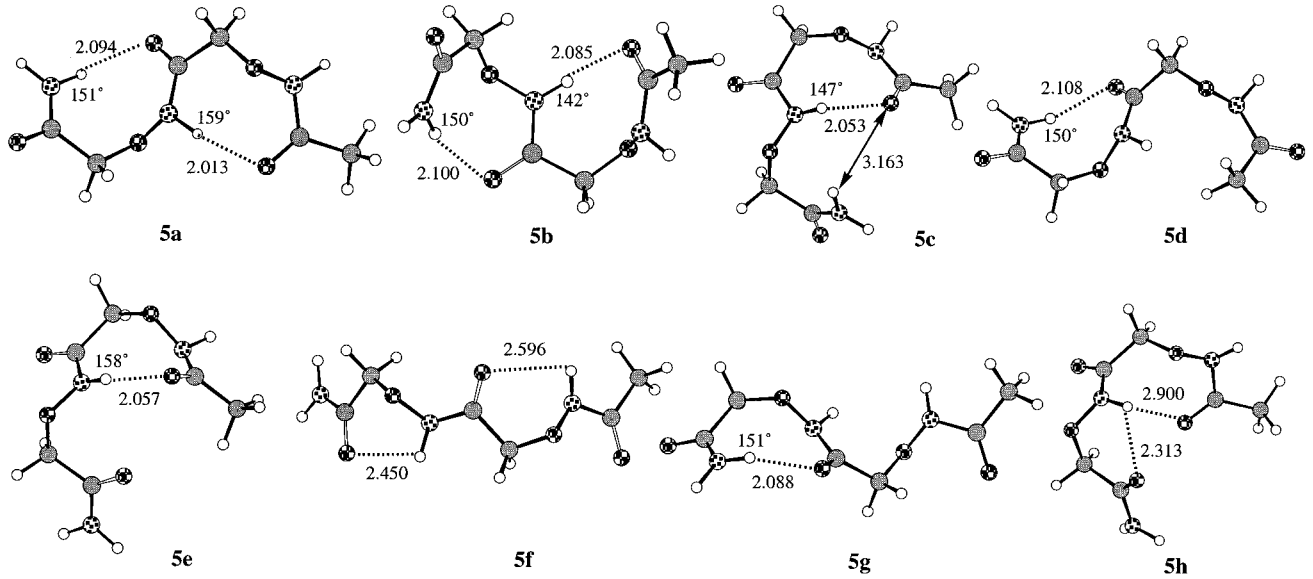

Figure 5. HF/6-31G** optimized conformers of oxa-tripeptide model **5**.

Table 3. Calculated Relative Energies (kcal/mol) of Conformers of Oxa-Tripeptide Models **5** and **6**

	gas phase		solv. SCIPCM, $\epsilon = 4.1$	
conf.	HF/6-31G**	MP2/6-31G**	HF/6-31G**	MP2/6-31G**[a]
		tripeptide model **5**		
5a	0.0	0.0	0.0	0.0
5b	0.7	0.6	0.9	0.8
5c	3.5	4.0	2.8	3.3
5d	6.2	6.2	5.7	5.7
5e	7.4	7.0	6.7	6.3
5f	7.7	11.0	5.6	8.9
5g	4.5	5.4	3.6	4.5
5h	6.9	7.4	6.0	6.5
		tripeptide model **6**		
6a	0.0	0.0	0.0	0.0
6b	0.7	1.1	0.9	1.3
6c	1.1	2.0	1.4	2.3
6d	2.2	1.2	2.6	1.6

[a] MP2/6-31G** (Gas Phase)-HF/6-31G** (Gas Phase) + HF/6-31G** (SCIPCM).

Table 4. Calculated Dipole Moment (Debye) and Relative Energies (kcal/mol) of Conformers of Oxa-Pentapeptide Models **7**

	gas phase		solv. SCIPCM, $\epsilon = 4.1$	
conf.	dipole	HF/6-31G**	HF/6-31G**	B3LYP/6-31G**
7a	14.6	0.0	0.0	0.0
7b	1.1	3.1	7.5	3.9
7c	20.2	23.3		
7d	4.2	12.5		

Several structures were further studied by the quantum mechanics method. These include the contiguous C8 helical structure,[37] the most stable "cyclic" structure, a 12-helix, and a 10/12-mixed helix. These structures are given in Figure 7.

The helical structure **7a** was found to be most stable with each level of the quantum mechanics calculation. This structure has some unique features: (1) The backbone forms a right-handed helical structure with four contiguous C8 units. (2) The three C8 units at the *N*-terminus form stronger hydrogen bonds than the *C*-terminus one as judged by the O- - -H bond length. This is explained by the fact that the *C*-terminus amide lacks an *N*-alkoxyl group, different from the other three amides. The *N*-alkoxyl group increases the ability of hydrogen bond formation by the amide. (3) The methyl side chains in **7a** alternate on opposite sides of the helix with a distance of 6.5 Å between those at positions i and $i + 2$, the pattern being reminiscent of a twisted parallel β-sheet found in proteins. (4) The amide carbonyl group at position $i + 2$ is twisted $+50°$ from the one at position i, which suggests a 1.8_8 helix or a twisted 2_8 helix with two residues per helical turn.

The most stable structure by the AMBER94* calculation (**7b**) is less stable than **7a** by 3.1 and 7.9 kcal/mol in the gas phase and $CHCl_3$, respectively, with the HF/6-31G* method, and is 4 kcal/mol less stable in $CHCl_3$ by the B3LYP/6-31G* method. This structure can be derived from **7a** by converting the first and third C8 units (from *C*-terminus) from right-handed to left-handed. The destabilization caused by the gauche methyl group in the two C8 units is partially compensated by the additional hydrogen bond between the two termina. Thus, one major reason for the destabilization of **7b** is poorer solvation compared to **7a**: it has a small dipole moment of 1.1 D compared to 14.6 D for **7a** and a smaller solvent-accessible surface. In addition, entropy, which is not calculated, is also expected to disfavor the structure. Other "cyclic" structures, which are similar to **7b** but higher in energy than **7b** by the AMBER94* calculations, should have the same feature. Therefore, it can be concluded that such "cyclic" structures are unfavorable in solution for homo-chiral oxa-peptides.

Structure **7c** has three contiguous 12-m-r hydrogen bonds, corresponding to the 12-helix of β-peptide. This is calculated to be about 23 kcal/mol less stable than **7a** in the gas phase due to several factors: (1) there is one less hydrogen bond; (2) the dihedral angles ψ are of unfavorable values of about 100°, while the most favorable value is about 0°; and (3) the carbonyl groups in **7c** are aligned along the helical axis, and there is a larger dipole/dipole repulsion than in **7a**.

We have found that a 10/12-mixed helix is intrinsically favored for β-peptides.[14b] However, this helix, **7d**, is calculated to be less stable than **7a** by about 12.5 kcal/mol in the gas phase. Two factors significantly contribute to the destabilization of

(37) Another contiguous C8 helical structure was also studied. This structure differs from **7a** in the conformation of two terminal C8 units, which are in unfavorable geometry of **4b**. It is predicted to be less stable than **7a** by about 1.4 kcal/mol both in the gas phase and in $CHCl_3$ solution.

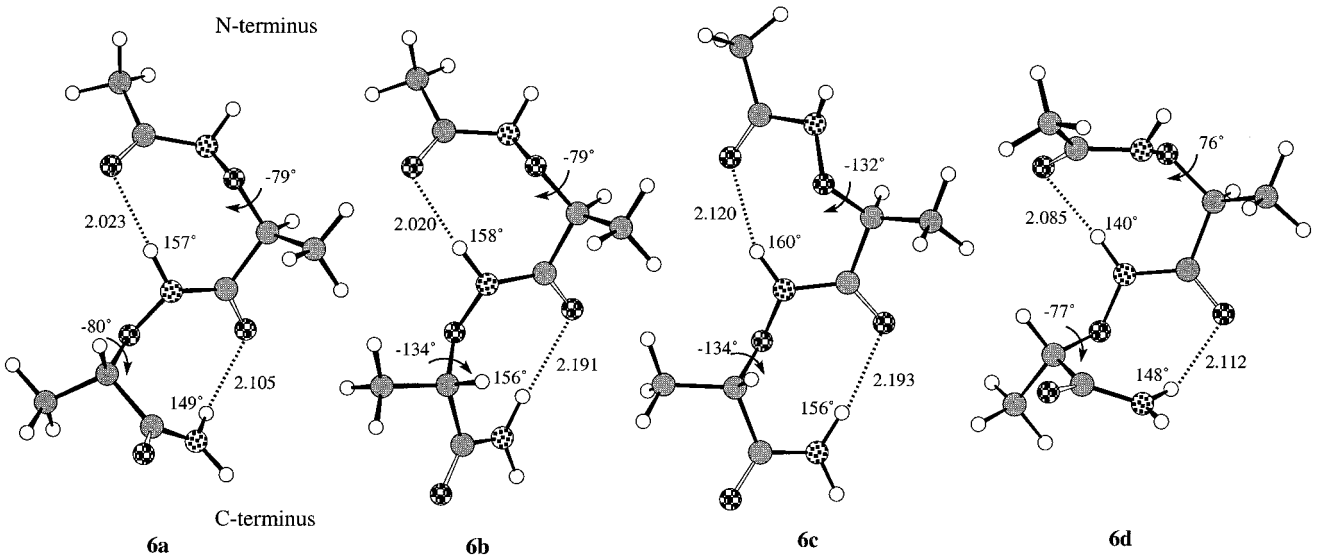

Figure 6. HF/6-31G** optimized conformers of oxa-tripeptide model **6**.

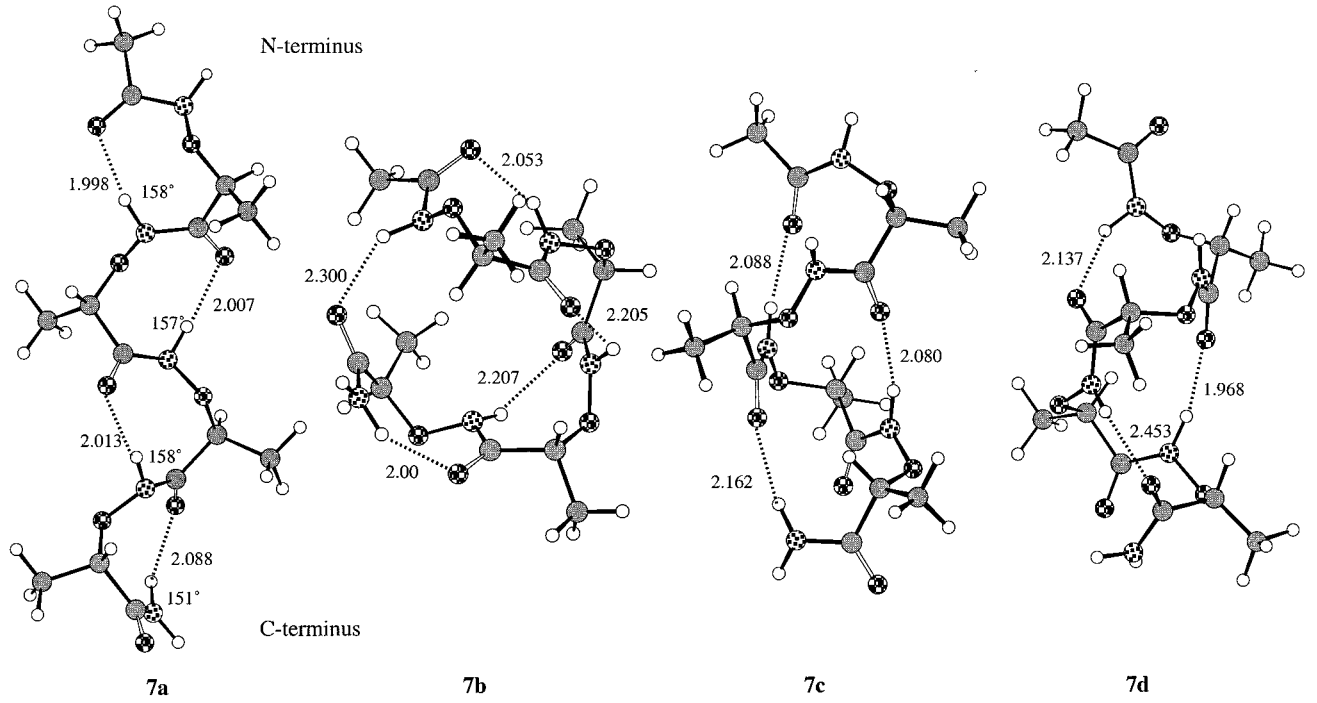

Figure 7. HF/6-31G* optimized conformers of oxa-pentapeptide model **7**.

7d: (1) it only allows two strong hydrogen bonds and one weak hydrogen bond and (2) the dihedral angle ψ has to be nearly 90°, which is highly destabilizing. We have not been able to calculate the solvent effect for **7d** (also **7c**) due to an unresolved error in potential energy surface, although it is expected to further destabilize **7d** with respect to **7a**.

A 14-helix has also been observed for some β-peptides. However, such a helix can be ruled out for oxa-peptides. First of all, there are two fewer hydrogen bonds in the 14-helix than in the 1.8_8-helix. Second, the large dihedral angles of ϕ and ψ for the 14-helix are unfavorable for oxa-peptides.

Thus, all the three types of helical structures, 12-helix, 14-helix, and 10/12-mixed helix, observed for β-peptides are highly unstable for oxa-peptides. The prediction that homo-(*S*)-oxa-peptides adopt a 1.8_8 helical structure like 7**a** is in agreement with available experimental observations, including IR, NMR, and CD spectra of several oligomers of aminoxy acids.[9b]

Summary

Conformational features of several oxa-peptide models have been studied by quantum mechanics calculations. The following results have been obtained:

(1) Oxa-peptides, like normal peptides, prefer anti conformation about the amide Csp2−N bond.

(2) In contrast to β-peptides, an oxa-peptide strongly prefers an 8-m-r hydrogen-bonded local structure (C8) between adjacent residues, which resembles a γ-turn found in proteins.

(3) The rotational direction of the C8 turn structure is determined by the chirality of the Cα center, because the alkyl side chain prefers to be anti to the N3−O4 bond instead of gauche.

(4) There is a cooperative effect for the formation of adjacent C8 structures. That is, the formation of one C8 structure will promote the formation of the adjacent C8 structures. In addition,

there is a small preference for the adjacent C8 structures turning in the same direction.

(5) Homo-(*S*)-oxa-peptides form a helical structure with contiguous C8 structures. Each turn of the helix contains about 1.8 aminoxy acid residues. The alkyl side chains alternate on opposite sides of the helix with a distance of 6.5 Å between those at positions i and $i + 2$. Helical structures found for β-peptides are quite unfavorable for oxa-peptides.

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Supporting Information Available: Calculated total energies of conformers of compounds **1**−**7** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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