Theoretical Studies of Monomer and Dimer of Cyclo[(−L-Phe^1-D-Ala^2−)$_n$] and Cyclo[(−L-Phe^1-D-^{Me}*N*-Ala^2−)$_n$] (n = 3−6)

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The monomer and dimer structures of cyclo[(−L-Phe^1-D-Ala^2)$_n$−] and cyclo[(−L-Phe^1-D-^{Me}*N*-Ala^2)$_n$−] (n = 3−6) were studied by using the semiempirical molecular orbital AM1 method and the density functional B3LYP method. The structural characteristics of these molecules were revealed, some of which are not yet confirmed experimentally. The influences of the substituents and ring size on molecular structure and the self-assembly process are discussed in detail. The inherent impetus for these molecules to self-assemble to polypeptide nanotubes is discussed.

Introduction

Research on nanometer-scale materials has become one of the most active fields in chemistry and material science. Because of certain unusual and unique properties, materials of nanometer size show broad potentials in many areas including chemistry, biochemistry, and material science. Among them, polypeptide nanotubes have recently attracted a great deal of attention because of their excellent ability to transport ions and molecules in a manner comparable with naturally occurring organo-nanotubes.

In early 1974, on the basis of the investigation of the structural characteristics of linear polypeptides formed by alternating D- and L-amino acids, de Santis and co-workers predicted the possibility of the formation of cylindrical cyclopolypeptides.[1] Unfortunately, early experiments could not verify the existence of any such polypeptide tubes, and it was not until 1993 that Ghadiri and co-workers[2] synthesized polypeptide tubes through self-assembling cyclopeptides formed by alternating eight D- and L-amino acid residues. In subsequent experiments, these investigators successfully synthesized cyclopeptide nanotubes constructed from six, eight, ten, and twelve different amino acid residues.[3−5] Compared with the ever-increasing interest in experimental syntheses, however, detailed theoretical understanding of the self-assembling organic nanotubes based on cyclic peptide architecture has lagged behind.[6] Using AM1 method, Gailer and Feigel[7] computed the energies of N-methylated cyclo[D,L-Ala]$_8$ and its dimers and demonstrated that for this type of molecule modeling cyclopolypeptides the difference in energy between parallel- and antiparallel-stacked dimer is almost zero with about 15 kJ/mol hydrogen-bonding energy in each. Using density functional methods, Jishi and co-workers[8] studied the equilibrium geometric structures for the monomer and dimer of cyclo[(Gly-D-Ala)$_4$], yet another cyclopolypeptide model compound. For cyclo[(Gln-D-Ala-Glu-D-Ala)$_2$], the first cyclopolypeptide found to self-assmble into polypeptide nanotubes, several research groups also conducted theoretical investigations. Among them, Lewis and co-workers[9] calculated the electronic structure and vibrational modes for cyclo[(Gln-D-Ala-Glu-D-Ala)$_m$] (m = 1−4) monomer, while both the Parrinello[10] and Fukasaku[11] groups computed the energy band structure for the cyclo[(Gln-D-Ala-Glu-D-Ala)$_2$] nanotube, concluding that this nanotube is a semiconductor with a rather wide band gap of around 4 eV. Although providing interesting theoretical descriptions for certain model cyclopolypeptide systems, the aforementioned computational studies have chosen two model compounds that are yet to be obtained experimentally; therefore, it would be rather difficult to verify their results. In addition, the side chains in the two model compounds are too simple to study the effect of side chains on the structure of cyclic polypeptides and their self-assembly processes. In particular, little is known about their microscopic properties, including their geometrical characteristics, energetics, and electronic structures. Therefore, it is of great importance to computationally study the structural characteristics and chemical properties using some actual experimentally obtained cyclic polypeptide systems. Such a study would not only facilitate the understanding of self-assembling organic molecules, but also improve experimental schemes to synthesize polypeptide nanotubes and even to design new organic nanotubes with biological activities.

This investigation applied the semiempirical molecular orbital method (AM1) and the density functional method (B3LYP) to cyclo[(−L-Phe^1-D-Ala^2−)$_n$] and cyclo[(−L-Phe^1-^{Me}*N*-Ala^2−)$_n$] (n = 3−6) polypeptide nanotube systems. The experimental synthesis and characterization concerning these systems have been reported.[12−14] It is the purpose of this work to study the detailed geometric structures, the driving force behind the self-assembly process for these types of molecules, and the effect of substituents as well as ring size on both the structure and the self-assembly process.

Model and Methods

Monomers of Cyclo[(−L-Phe^1-D-Ala^2−)$_n$] and Cyclo[(−L-Phe^1-D-^{Me}*N*-Ala^2−)$_n$]. Cyclo[(−L-Phe^1-D-Ala^2−)$_n$] takes on a planar, dinner-plate-shaped geometry consisting of an even number of alternating D- and L-amino acid residues connected head-to-tail. The initial geometry for the monomer cyclo[(−L-Phe^1-D-Ala^2−)$_n$] was first obtained using Insight II 95.0, a

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molecular graphics software package.[15] Each cyclic polypeptide was then optimized using the molecular mechanics of the Discover program contained within Insight II, which employs a CV force field and includes Morse cross-term interactions. Optimization stops when rms reaches 0.0001 kcal/mol thresholds.

The initial conformation for cyclo[(−L-Phe^1-D-^{Me}N-Ala^2−)$_n$] was constructed from the optimized cyclo[(−L-Phe^1-D-Ala^2−)$_n$] system. First, methyl groups replaced the hydrogen atoms that were connected directly to nitrogens of amino acids in cyclo[(−L-Phe^1-D-Ala^2−)$_n$]. The same optimization procedure was then applied to the initially constructed cyclo[(−L-Phe^1-D-^{Me}N-Ala^2−)$_n$] structure.

Dimers of Cyclo[(−L-Phe^1-D-Ala^2−)$_n$] and Cyclo[(−L-Phe^1-D-^{Me}N-Ala^2−)$_n$]. In this study, nanotube systems were modeled only as dimers of cyclo[(−L-Phe^1-D-Ala^2−)$_n$] and cyclo[(−L-Phe^1-D-^{Me}N-Ala^2−)$_n$]. They were chosen not only because it would be computationally impractical to model any polymers of these cyclopeptides higher than a dimer in this work, but also because it is believed that the structure and function of a dimer can be representative of polypeptide nanotubes, including the effect of the cyclic ring size, side-chains, and stacking scheme of the rings on the formation of nanotubes. As a matter of fact, it has been confirmed experimentally that cyclo[(−L-Phe^1-D-^{Me}N-Ala^2−)$_4$] can form only a dimer and cannot be further stretched to become a nanotube.

Methods. The dimers were constructed by bringing together two identical cyclic polypeptide monomers along the C_4 axis perpendicular to the plane of the rings, in which the carbonyl oxygen of an amino acid in a monomer and the hydrogen of N−H of an amino acid in another monomer are located within the range of a typical hydrogen bond. For the monomers with four ($n = 4$) cyclic polypeptides, both the parallel and antiparallel stacking schemes were considered. For the monomers with polypeptide numbers $n = 3$, 5, and 6, only the antiparallel stacking was studied. All such constructed dimers were first optimized with the Insight II Discover program.

On the basis of the conformations obtained by the Discover program, both monomers and dimers were further studied using quantum mechanical methods. All of the monomers and dimers were optimized, and the vibration frequency calculations for monomers and dimers of $n = 4$ were performed with the semiempirical molecular orbital method AM1.[16] Conformations with $n = 4$ were also investigated using the density functional B3LYP method. The B3LYP[17] scheme is a Beck's three parameter hybrid method using the Lee−Yang−Parr correlation function,[18] which includes both local and nonlocal terms, and a Vosko−Wilk−Nusair correlation function[19] referred to as local spin density correlation. A 6-31G basis set was used with the B3LYP method to optimize the geometric structures for all comformations with $n = 4$, and then B3LYP/6-31G*//B3LYP/6-31G single point calculations followed. All calculations were performed using Gaussian 94[20] and Gamess[21] on an Intel PC computer configured with 512 Mb of RAM and 23 Gb of disk space. Because of the sheer size of the systems investigated in this work (240−264 atoms including over 100 heavy atoms), the computational exploring of solvation effect far exceeds the computer power available to us and, hence, is not included.

Results and Discussion

Cyclo[(−L-Phe^1-D-Ala^2−)$_4$] and Cyclo[(−L-Phe^1-D-^{Me}N-Ala^2−)$_4$]. *Results from the B3LYP Density Functional Method.* The monomers consisting of four polypeptides and their dimers, stacked by forming hydrogen bonds, were optimized with the B3LYP/6-31G method. The 6-31G* basis set was then employed in energy calculations of single points. The choice to not use it in the optimizing step is based on the following. First, the use of the 6-31G* basis set would drastically increase the number of basis functions from 1376 and 1480 to 2144 and 2296 for cyclo[(−L-Phe^1-D-Ala^2−)$_4$] and cyclo[(−L-Phe^1-D-^{Me}N-Ala^2−)$_4$], respectively, making geometry optimization impractical on the computers available to us. Second, it was found in this study that the inclusion of the polarization d-functions did not alter geometric structures substantially from those without the d-functions included. Table 1 compares some key geometric parameters for three different cyclopolypeptide monomers, and one can see that the ones obtained with the d-functions included[10] are rather similar to those calculated in this work without such functions.

TABLE 1: Geometric Parameters of Ala Residue in Monomer

			this work	
	standard geometry[a]	Jishi's work[10] cyclo-[(−Gly-D-Ala)$_4$−]	cyclo-[(−Phe-D-Ala)$_4$−]	cyclo-[(−Phe-D-^{Me}N-Ala)$_4$−]
		Lengths (Å)		
C═O	1.23	1.23	1.26	1.26
C−N	1.32	1.34	1.35	1.36
N−H	1.00	1.02	1.01	
N−C$^\alpha$	1.47	1.44	1.46	1.49
C−C$^\alpha$	1.53	1.51	1.53	1.53
		Angles (deg)		
C$^\alpha$CN	114	117	116	116
C$^\alpha$CO	121	119	121	122
NCO		124	123	123
C$^\alpha$NC	123	120	123	117
C$^\alpha$NH		116	115	
CNH	123	124	122	
φ		144	149	127
ψ		−138	−149	−108
ω		176	176	173

[a] Corey, R. B.; Pauling, L. *Proc. R. Soc. London, Ser. B.* **1953**, *141*, 10−20.

The optimized geometric structures are shown in Figures 1 and 2.

At the level of B3LYP/6-31G, the cyclo[(−L-Phe^1-D-Ala^2−)$_4$] monomer has −2902.03137 au in energy and possesses C_4 symmetry. It can be seen that the side chains on phenylalanine and alanine residues (i.e., methyl groups and phenyl rings) are located along the rim, while the NH and CO groups form almost a right angle of 90° (±3°) with respect to the plane of the ring. Despite a similar C_4 symmetry, the conformation for the optimized cyclo[(−L-Phe^1-D-^{Me}N-Ala^2−)$_4$] is distorted to a certain extent compared to that for cyclo[(−L-Phe^1-D-Ala^2−)$_4$]. This distortion can be attributed to the existence of N−CH_3 in all methyl-substituted alanine amino acid residues. First, the angles of NH and CO with respect to the ring plane depart farther than that found in cyclo[(−L-Phe^1-D-Ala^2−)$_4$], though not enough to affect the formation of intermolecular hydrogen bonds. Second, the distortion angle, ω, of phenylalanine and alanine residues in dimers about the N−C peptide bonds is 171.8° and −167.9°, respectively. This is about a ±10° departure from the normal value of 180° for ω. This indicates a larger distortion in the peptide C−N double bonds and hence leads to the increase in ring strain. Fortunately, in this polypeptide, which consists of eight alternating D- and L-amino acids, the existence of methyl groups does not cause a breakdown of the ring structure because keeping a ring conformation is still an important geometric characteristic of cyclo[(−L-Phe^1-D-^{Me}N-

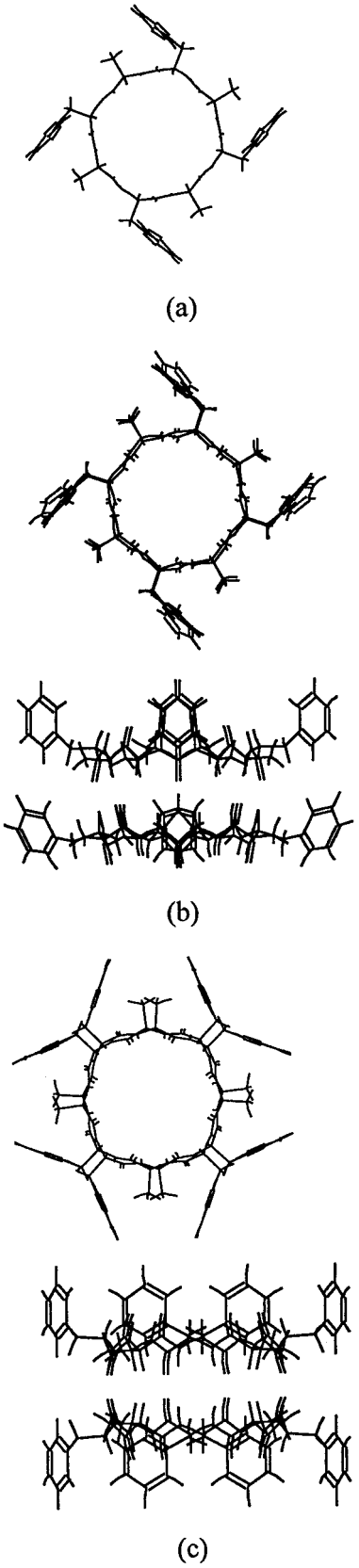

Figure 1. The conformations of monomer (a) and parallel (b) and antiparallel (c) dimer of cyclo[(−L-Phe^1-D-Ala^2−)$_4$].

Ala^2−)$_4$]. It is noted that a cyclic conformation and an almost perpendicular arrangement of the functional groups NH and CO relative to the ring plane should make it possible for the cyclo[(−L-Phe^1-D-Ala^2−)$_4$] monomer to aggregate and form nanotubes through intermolecular hydrogen bonding.

Table 2 lists the energies in hartrees (E), the interaction energies (IE) in kJ/mol with the correction of basis set superimposing error (BSSE), the intermonomer separation (d_{mono}), the intermolecular N···O distance (d_{N-O}) in angstroms, and the angle of NHO (θ) in degrees. It has been shown experimentally[22] that the distance between subunits for cyclic polypeptides is around 4.7−4.8 Å and the intermolecular N···O distance (d_{N-O}) is between 2.70 and 2.90 Å, while the NHO angles are in the range of 165°−175°. The results presented in this work are in agreement with these experimental findings. When one compares interaction energies, the energy for the dimerization of a parallel arrangement is slightly higher than that for an antiparallel-stacked system. This is also in agreement with the results predicted by the experimental study.[9] In addition, it should, however, be noted that IE_{BSSE} at the B3LYP/6-31G* level of theory is around 190 kJ/mol (see the fourth column in Table 2), which is translated into about 24 kJ/mol of energy for each hydrogen bond in these systems if no other interactions among non-N−H···O groups are considered. The value of 24 kJ/mol is, of course, close, but it is a bit higher than the commonly accepted 20 kJ/mol for a typical hydrogen bond. With the model and level of theory employed in this study, this value of about 24 kJ/mol again strongly confirms that formation of the N−H···O hydrogen bonds is the primary driving force in stabilizing the polypeptide dimers.

Results from the AM1 Method. The semiempirical molecular AM1 method was applied to the monomers of cyclo[(−L-Phe^1-D-Ala^2−)$_4$] and cyclo[(−L-Phe^1-D-^{Me}*N*-Ala^2−)$_4$] and their dimers, both parallel- and antiparallel-stacked. The AM1 optimized geometric structures are displayed in Figures 3 and 4.

The antiparallel-stacked dimer of cyclo[(−L-Phe^1-D-Ala^2−)$_4$] possesses D_4 symmetry with an enthalpy of formation of −1894.7 kJ/mol and an energy of intermolecular interaction of −145.9 kJ/mol. The parallel-stacked dimer, however, shows a C_4 symmetry with an enthalpy of formation of −1870.9 kJ/mol and an energy of intermolecular interaction of −137.6 kJ/mol. These data indicate that the antiparallel-stacking scheme is favored over the parallel one. Energetically, antiparallel-stacking produces a stronger intermolecular attraction. Geometrically, a better perpendicularity of the CO and NH groups relative to the ring plane is also achieved in this fashion of packing. These predictions about stacking preference are in good agreement with that made with the B3LYP/6-31G method and are also suggested in some experimental designs and models.[7−9]

The antiparallel stacking of cyclo[(−L-Phe^1-D-^{Me}*N*-Ala^2−)$_4$] can take on two different forms as shown in Figure 4: one is the antiparallel configuration I that is formed through intermolecular hydrogen bonding, and the other is the antiparallel configuration II that does not seem to involve intermolecular O···H−N hydrogen bonding because of the replacement of the hydrogens in all N−H groups with methyl groups. This and the parallel stacking (the configuration III in Figure 4) can only form very weak O···HC hydrogen bonds. Table 3 lists some major energetic and geometric parameters and clearly shows that the antiparallel-stacking scheme I involving intermolecular hydrogen bonds is most favored because its IE is almost four times that for scheme II and five times that for scheme III (the parallel one). Moreover, the intermonomer separation (d_{mono}) and intermolecular N···O distance (d_{N-O}) for configuration I are fairly close to the experimental values. Note also that blocking methyl groups in configurations II and III greatly separate the two monomers and hence reduce the interaction between them.

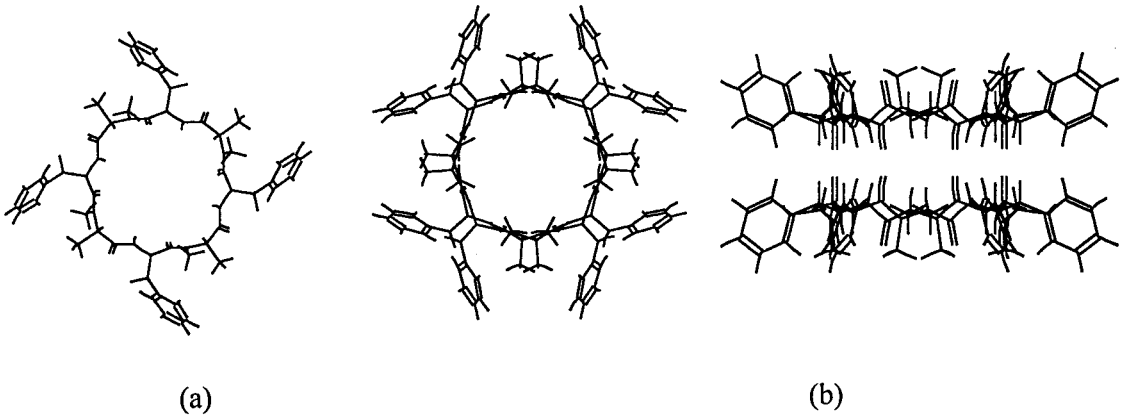

Figure 2. The conformations of monomer (a) and antiparallel dimer (b) of cyclo[(−L-Phe^1-D-^{Me}*N*-Ala^2−)$_4$].

TABLE 2: The Main Properties of Dimers for Cyclo[(−L-Phe^1-D-Ala^2−)$_4$] and Cyclo[(−L-Phe^1-D-^{Me}*N*-Ala^2−)$_4$]

	E (hartree)	IE_{BSSE} (kJ/mol)	IE_{BSSE}[a] (kJ/mol)	d_{mono} (Å)	d_{N-O} (Å)	θ (deg)
parallel cyclo[(−L-Phe^1-D-Ala^2−)$_4$]$_2$	−5804.155 41	−226.1	−183.8	∼4.84	2.97	∼156.9
antiparallel cyclo[(−L-Phe^1-D-Ala^2−)$_4$]$_2$	−5804.177 01	−249.0	−199.1	∼4.82	∼2.88	163.8
antiparallel cyclo[(−L-Phe^1-D-^{Me}*N*-Ala^2−)$_4$]$_2$	−6118.452 71	−246.4	N/A[b]	∼4.84	2.85	166.8

[a] Obtained with B3LYP/6-31G*//B3LYP/6-31G single-point calculations. [b] Not available because of the limits of our computer power.

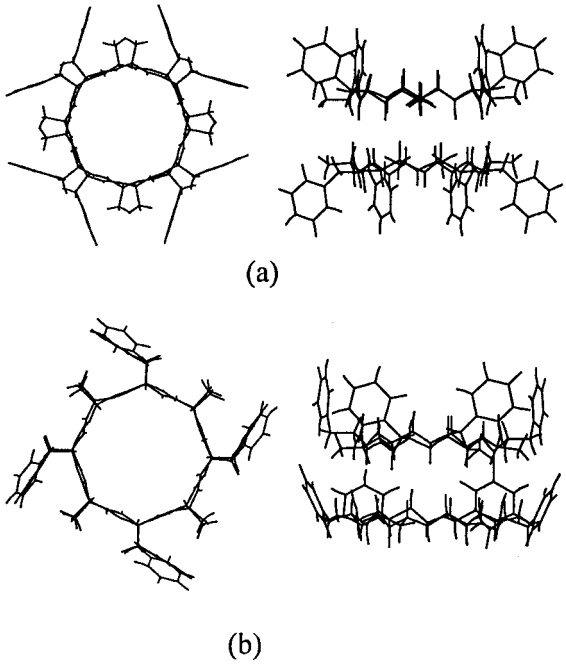

Figure 3. The conformations of dimers for cyclo[(−L-Phe^1-D-Ala^2−)$_4$]: (a) antiparallel; (b) parallel.

Harmonic vibrational frequencies were also computed for all of the monomers and dimers. The N−H stretching modes in the cyclo[(−L-Phe^1-D-Ala^2−)$_4$] monomer and its parallel- and antiparallel-stacked dimers are 3457.8−3460.3, 3423.8−3457.3, and 3432.2−3455.4 cm^{-1}, respectively. The N−H stretching modes for the cyclo[(−L-Phe^1-D-^{Me}*N*-Ala^2−)$_4$] monomer and its parallel III, antiparallel II, and antiparallel I dimers are 3456.8−3458.2, 3453.3−3459.5, 3451.4−3452.7, and 3419.2−3423.0 cm^{-1}, respectively. The obvious downward shift found in N−H stretching frequencies is primarily due to hydrogen bonding in supramolecular cyclo[(−L-Phe^1-D-Ala^2−)$_4$]$_2$ and in the antiparallel I model of cyclo[(−L-Phe^1-D-^{Me}*N*-Ala^2−)$_4$]$_2$ dimers. Although one cannot strictly compare the quantum-mechanically calculated vibrational frequencies of a molecule to experimentally observed ones, the calculated harmonic frequencies in this work nevertheless are quantitatively reasonable considering the experimentally observed 3309 cm^{-1} N−H stretching band in a solution IR spectrum.[7−9] Moreover, it is noted that the calculated vibrational intensity for the N−H stretching mode in parallel- and antiparallel-stacked cyclo[(−L-Phe^1-D-Ala^2−)$_4$], as well as antiparallel I cyclo[(−L-Phe^1-D-^{Me}*N*-Ala^2−)$_4$], is obviously increased relative to that of the monomer. For example, the calculated vibrational intensities of the N−H stretching mode in the cyclo[(−L-Phe^1-D-^{Me}*N*-Ala^2−)$_4$] monomer and antiparallel I mode are 316.3 and 1911.6 kM/mol at 3458.2 and 3422.7 cm^{-1}, respectively. This is in

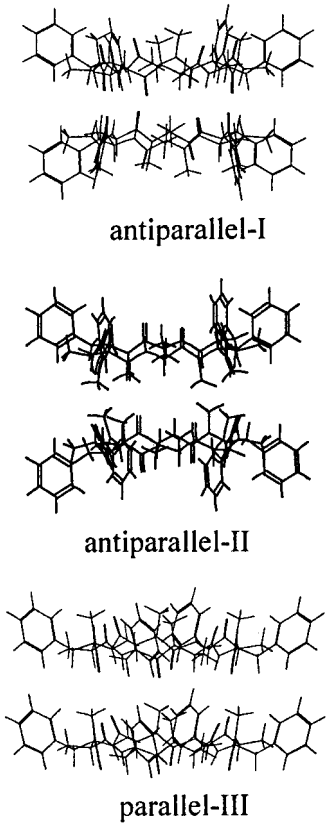

Figure 4. The conformations of dimers for cyclo[(−L-Phe^1-D-^{Me}*N*-Ala^2−)$_4$].

TABLE 3: The Main Properties of Dimers for Cyclo[(−L-Phe[1]-D-[Me]*N*-Ala[2]−)$_4$]

	E (hartree)	IE (kJ/mol)	diameter (Å)	d_{mono} (Å)	d_{N-O} (Å)
antiparallel I	−864.166 37	−127.9	∼8.6	∼4.87	3.06
antiparallel II	−864.135 25	−33.2	∼8.7	∼6.20	4.30
parallel III	−864.130 73	−26.8	∼8.8	∼6.21	4.49
refs 7−9			∼7.5	∼4.80	∼2.95

accordance with the observed N−H stretching modes in infrared spectra. Other than some stretches such as C−H and C═O, most normal modes are hardly localized in any specific chemical functional group.

It is therefore reasonable to conclude that (a) because of very small IE but rather large d_{mono} it is very unlikely, if not impossible, for the (−L-Phe[1]-D-[Me]*N*-Ala[2]−)$_4$ molecule to congregate according to schemes II and III, (b) methyl group replacement actually plays a vital role in blocking congregation and as such it greatly reduces the ability of the (−L-Phe[1]-D-[Me]*N*-Ala[2]−)$_4$ molecule to form polypeptide nanotubes by self-assembling, (c) the (−L-Phe[1]-D-[Me]*N*-Ala[2]−)$_4$ molecule can form a dimer through intermolecular hydrogen bonding and antiparallel stacking, (d) it is the hydrogen bonding between the oxygens of carbonyl groups in one monomer and the hydrogens of N−H groups in another monomer that is the intrinsic driving force that makes it possible for cyclic polypeptides to form nanotubes by self-assembling, and (e) other intermolecular attractive forces also greatly help to stabilize the nanotubes. These conclusions are consistent with the fact that the (−L-Phe[1]-D-[Me]*N*-Ala[2]−)$_4$ polypeptide can only form a dimer.[7−9]

The effect of entropy was also studied in this work. It was found that the entropy is 2.86 and 2.73 kJ/(K mol), while the entropy reduction is 0.304 and 0.300 kJ/(K mol) for anitiparallel and parallel dimers, respectively. Even though it is recognized that self-assembly may be an entropy-reducing process, it can still occur naturally because of a substantial amount of attractive forces.

Cyclo [(−L-Phe[1]-D-Ala[2]−)$_n$] and Cyclo[(−L-Phe[1]-D-[Me]*N*-Ala[2]−)$_n$] with n = 3, 5, and 6. Three monomers of cyclo[(−L-Phe[1]-D-Ala[2]−)$_n$] with n = 3, 5, and 6 optimized with the AM1 method are shown in Figure 5.

Their heat of formation is −658.0, −1096.7, and −1313.9 kJ/mol, respectively. They all have C_n symmetry with an inner diameter around 7, 11, and 13 Å, respectively. The skeleton functional groups are almost perpendicular to the ring plane, while all amino acid residues are distributed outward along the rim. Compared to cyclo[(−L-Phe[1]-D-Ala[2]−)$_4$], the size of the ring affects the configuration of cyclo[(−L-Phe[1]-D-Ala[2]−)$_n$] with n = 3, 5, and 6 more or less strongly. For example, the deviation of the distortion angle ω from 180° in the three rings is greater than that in cyclo[(−L-Phe[1]-D-Ala[2]−)$_4$], varying from 2−4° average to 7° maximum. Because they possess the geometric characteristics for forming polypeptide nanotubes, cyclo[(−L-Phe[1]-D-Ala[2]−)$_{n=3,5,6}$] polypeptides may self-assemble into nanotubes through intermolecular O···H−N hydrogen bonds along the C_n axis. Figure 6 shows the configurations of the dimers formed from two antiparallel-stacked cyclo[(−L-Phe[1]-D-Ala[2]−)$_{n=3,5,6}$] monomers. Their interaction energy, IE, is −104.3, −157.7, and −181.4 kJ/mol, respectively.

Unfortunately, the attempt to optimize cyclo[(−L-Phe[1]-D-[Me]*N*-Ala[2]−)$_n$] (n = 3, 5, and 6) using both the molecular mechanics and AM1 methods was unsuccessful in the sense that only a twisted nonplanar cyclic [(−L-Phe[1]-D-[Me]*N*-Ala[2]−)$_{n=3,5,6}$] could be obtained computationally. The failure to obtain a planar cyclic [(−L-Phe[1]-D-[Me]*N*-Ala[2]−)$_{n=3,5,6}$] may have resulted from the combined effect of both the methyl group substitution and the change in ring size, because the existence of methyl groups worsens the distortion of a cyclopeptide planar ring. Too small of a ring size (n = 3) increases its tension, while too large of a ring size (n > 4) makes it too flexible to keep a planar configuration. These rationales are consistent with the finding in ref 9 that no β-sheet characters were observed for n = 6, while there was only one broad NMR signal recorded for the n = 5 entity. It should be further noted that there are no experimental findings to support the existence of the cyclo[(−L-Phe[1]-D-[Me]*N*-Ala[2]−)$_{n=3,5,6}$] dimers.

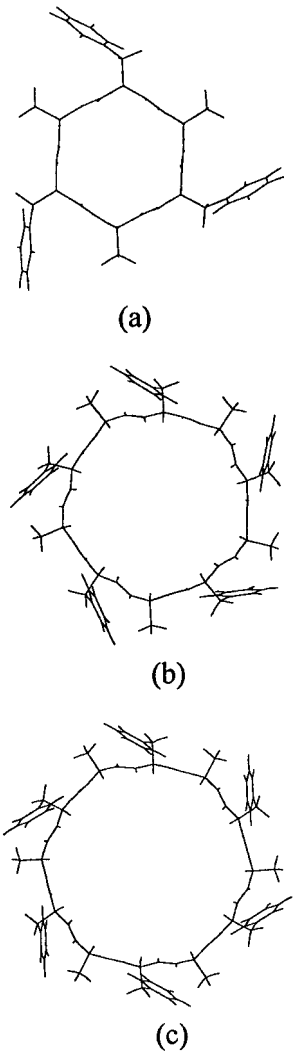

Figure 5. The conformations for cyclo[(−L-Phe[1]-D-Ala[2]−)$_n$] monomers: (a) n = 3; (b) n = 5; (c) n = 6.

Conclusion

Cyclo[(−L-Phe[1]-D-Ala[2]−)$_{n=3-6}$] and cyclo[(−L-Phe[1]-D-[Me]*N*-Ala[2]−)$_{n=3-6}$] and their dimers were investigated in this work by means of the semiempirical molecular orbital AM1 and density functional B3LYP methods. This investigation reinforces the following experimental findings: (a) a perfect planar cyclic ring, good perpendicularity of NH and CO groups to the ring plane, and outwardly expanded side groups are the conditions necessary for the cyclo[(−L-Phe[1]-D-Ala[2]−)$_{n=4}$] polypeptides to self-assemble into nanotubes; (b) the intrinsic driving force in their self-assembly is their ability to form hydrogen bonds between the monomers stacked along the C_4 axes; and (c) because of blocking methyl groups, cyclo[(−L-Phe[1]-D-[Me]*N*-

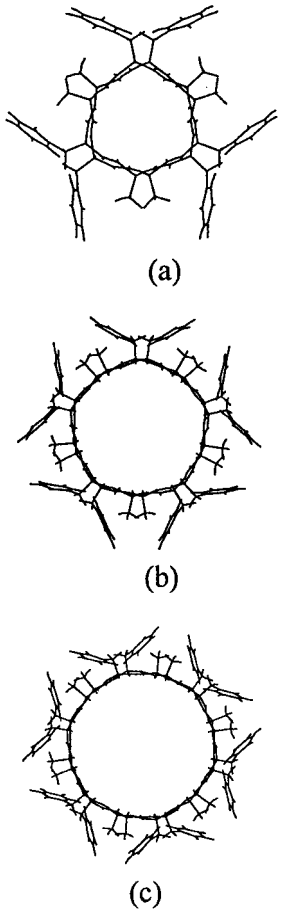

Figure 6. The conformations for cyclo[(−L-Phe^1-D-Ala^2−)$_n$] dimers: (a) $n = 3$; (b) $n = 5$; (c) $n = 6$.

Ala^2−)$_{n=4}$] only congregates to a dimer. More importantly, this theoretical study provides some insights into the formation of polypeptide nanotubes that are yet to be verified experimentally: (a) the antiparallel stacking scheme is favored over the parallel one; (b) the replacement of hydrogens in N−H in alanine residues with methyl groups leads to an increase in the ring strain and the deformation of cyclic structure; (c) because of the dual action of blocking methyl groups and the size of the ring, cyclo[(−L-Phe^1-D-^{Me}*N*-Ala^2−)$_{n=3,5,6}$] does not possess a planar cyclic conformation, and as such it can no longer hold the basic structural character of keeping a planar ring shape and consequently it cannot undergo a self-assembling process; and (d) because cyclo[(−L-Phe^1-D-Ala^2−)$_{n=3,5,6}$] possesses similar structural characteristics as cyclo[(−L-Phe^1-D-Ala^2−)$_{n=4}$], it is expected that this system should be able to form nanotubes by self-assembling.

Although conducted under gas-phase conditions, this investigation nevertheless provides a rather satisfactory theoretical description of the monomer and dimer structures of cyclo[(−L-Phe^1-D-Ala^2−)$_n$] and cyclo[(−L-Phe^1-D-^{Me}*N*-Ala^2−)$_n$] ($n = 3-6$) and should greatly facilitate the understanding of the self-assembling process of polypeptide nanotubes.

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References and Notes

(1) de Santis, P.; Morosetti, S.; Rizzo, R. *Macromolecules* **1974**, *7*, 52.
(2) Ghadiri, M. R.; Granja, J. R.; Milligan, R. A.; McRee, D. E.; Khazanovich, N. *Nature* **1993**, *366*, 324.
(3) Sun, X. C.; Lorenzi, G. P. *Helv. Chim. Acta* **1994**, *77*, 1520.
(4) Granja, J. R.; Ghadiri, M. R. *J. Am. Chem. Soc.* **1994**, *116*, 10785.
(5) Khazanovich, N.; Granja, J. R.; McRee, D. E.; Milligan, R. A.; Ghadiri, M. R. *J. Am. Chem. Soc.* **1994**, *116*, 6011.
(6) Lewis, J. P.; Pawley, N. H.; Sankey, O. F. *J. Phys. Chem. B* **1997**, *101*, 10576.
(7) Gailer, C.; Feigel, M. *J. Comput.-Aided. Mol. Des.* **1997**, *11*, 273.
(8) Jishi, R. A.; Flores, R. M.; Valderrame, M.; Lou, L.; Bragin, J. *J. Phys. Chem. A* **1998**, *102*, 9858.
(9) Lewis, J. P.; Pawley, N. H.; Sankey, O. *J. Phys. Chem. B* **1997**, *101*, 10576.
(10) Carloni, P.; Andreoni, W.; Parrinello, M. *Phys. Rev. Lett.* **1997**, *79* (4), 761.
(11) Fukasaku, K.; Takeda, K.; Shiraishi, K. *J. Phys. Soc. Jpn.* **1998**, *67* (11), 3752.
(12) Ghadiri, M. R.; Kobayashi, K.; Granja, J. R.; Chadha, R. K.; McRee, D. E. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 93.
(13) Kobayashi, K.; Granja, J. R.; Ghadiri, M. R. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 95.
(14) Clark, T. D.; Buriak, J. M.; Kobayashi, K.; Isler, P.; McRee, D. E.; Ghadiri, M. R. *J. Am. Chem. Soc.* **1998**, *120*, 8949.
(15) *Insight II 95*; Biosym/MSI Co.: San Diego, CA.
(16) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F. *J. Am. Chem. Soc.* **1985**, *107*, 3902.
(17) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.
(18) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
(19) Vosko, S. H.; Wilk, L.; Nusair, M. *Can. J. Phys.* **1980**, *58*, 1200.
(20) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. *Gaussian 94*, revision A.1; Gaussian, Inc.: Pittsburgh, PA, 1995.
(21) Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Elbert, T.; Gordon, M. S.; Jensen, J. J.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S.; Windus, T. L.; Dupuis, M.; Montgomery, J. A. *J. Comput. Chem.* **1993**, *14*, 1347 (GAMESS).
(22) Hartgerink, J. D.; Granja, J. R.; Milligan, R. A.; Ghadiri, M. R. *J. Am. Chem. Soc.* **1996**, *118*, 43.