JOC Article

Zipper-Featured δ-Peptide Foldamers Driven by Donor−Acceptor Interaction. Design, Synthesis, and Characterization

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Donor−acceptor interaction between electron-rich 1,5-dioxynaphthalene (DAN) and electron-deficient pyromellitic diimide (PDI) has been utilized to induce the formation of a new kind of zipper-featured δ-peptide foldamers. Seven L-ornithine-based δ-peptides **1a**−**g**, in which one to three DNA and PDI units are incorporated to the two ends of the peptide backbones, respectively, have been designed and prepared by the standard liquid-phase synthetic method. ^{1}H NMR, UV−vis, and fluorescent quenching studies reveal that all the δ-peptides adopt folding conformations in nonpolar chloroform and polar DMF as a result of intramolecular donor−acceptor interaction between the DAN and PDI units. The folding states become more compact for the peptide skeletons possessing more donor−acceptor interacting sites. Variable-temperature UV−vis experiments indicate that, although the folding is a dynamic process, the folding state can remain even at 150 °C in DMF. Circular dichroism (CD) investigations reveal that the new generation of δ-peptides have similar folding patterns. A zipper-featured folding motif has been proposed for the new generation of δ-peptide foldamers. Molecular modeling has generated two most stable folding states for the longest δ-peptide **1g**, with an energy difference of 26.80 kcal/mol.

Introduction

Inspired by the remarkable variety of well-organized nanoarchitectures found in biomacromolecules such as proteins and nucleic acids, in the past decade there has been intensive interest in the design of synthetic oligomers that adopt well-defined folding and compact conformations.[1] Lehn et al. have used transition metal−ligand coordination to build extended helical structures from polyheterocyclic strands.[2] Moore et al. have utilized the solvophobic interaction to induce the formation of folded nanotubes from phenylacetylene oligomers.[3] Possibly due to their incomparable importance in natural helical and multiple helical systems, hydrogen bonds have received especially great attention in the development of artificial folded species and a large number of hydrogen bond-mediated artificial α-peptides and β-peptide foldamers have been described.[4] Moreover, foldamers based on synthetic γ-peptides,[5] peptoid oligomers,[6] and heterocyclic ureas[7] have also been reported. However, δ-peptides with well-defined folded conformation have not been reported, possibly due to the increased flexibility of δ-peptide backbones.[8]

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(1) For review articles, see: (a) Bassani, D. M.; Lehn, J.-M.; Baum, G.; Fenske, D. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1845. (b) Seebach, D.; Matthews, J. L. *Chem. Commun.* **1997**, 2015. (c) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173. (d) Nowick, J. S. *Acc. Chem. Res.* **1999**, *32*, 287. (e) Katz, T. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 1921. (f) Cubberley, M. S.; Iverson, B. L. *Curr. Opin. Chem. Biol.* **2001**, *5*, 650. (g) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893. (h) Seebach, D.; Beck, A. K.; Brenner, M.; Gaul, C.; Heckel, A. *Chimia* **2001**, *55*, 831. (i) Gong, B. *Chem. Eur. J.* **2001**, *7*, 4336. (j) Zhao, D.; Moore, J. S. *Chem. Commun.* **2003**, 807.

(2) For recent examples, see: (a) Berl, V.; Huc, I.; Khoury, R. G.; Krische, M. J.; Lehn, J.-M. *Nature* **2000**, *407*, 720. (b) Barboiu, M.; Lehn, J.-M. *PNAS* **2002**, *99*, 5201. (c) Petitjean, A.; Cuccia, L. A.; Lehn, J.-M.; Nierengarten, H.; Schmutz, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 1195.

(3) For recent examples, see: (a) Prince, R. B.; Moore, J. S.; Brunsveld, L.; Meijer, E. W. *Chem. Eur. J.* **2001**, *7*, 4150. (b) Oh, K.; Jeong, K.-S.; Moore, J. S. *Nature* **2001**, *414*, 889. (c) Zhao, D.; Moore, J. S. *J. Am. Chem. Soc.* **2002**, *124*, 9996. (d) Hill, D. J.; Moore, J. S. *PNAS* **2002**, *99*, 5053. (e) Tanatani, A.; Hughes, T. S.; Moore, J. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 325. (f) Matsuda, K.; Stone, M. T.; Moore, J. S. *J. Am. Chem. Soc.* **2002**, *124*, 11836. (g) Wang, W.; Li, L.-S.; Helms, G.; Zhou, H.-H.; Li, A. D. Q. *J. Am. Chem. Soc.* **2003**, *125*, 1120.

(4) For recent examples, see: (a) Fisk, J. D.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **2000**, *122*, 5443. (b) Seebach, D.; Schreiber, J. V.; Abele, S.; Daura, X.; van Gunsteren, W. F. *Helv. Chim. Acta* **2000**, *83*, 34. (c) Langenhan, J. M.; Fisk, J. D.; Gellman, S. H. *Org. Lett.* **2001**, *3*, 2559. (d) Arvidsson, P. I.; Rueping, M.; Seebach, D. *Chem. Commun.* **2001**, 649. (e) Porter, E. A.; Weisblum, B.; Gellman, S. H. *J. Am. Chem. Soc.* **2002**, *124*, 7324.

(5) (a) Hanessian, S.; Luo, X.; Schaum, R.; Michnick, S. *J. Am. Chem. Soc.* **1998**, *120*, 8569. (b) Woll, M. G.; Lai, J. R.; Guzei, I. A.; Taylor, S. J. C.; Smith, M. E. B.; Gellman, S. H. *J. Am. Chem. Soc.* **2001**, *123*, 11077. (c) Seebach, D.; Brenner, M.; Rueping, M.; Jaun, B. *Chem. Eur. J.* **2002**, *8*, 573.

(6) (a) Kirshenbaum, K.; Barron, A. E.; Goldsmith, R. A.; Armand, P.; Bradley, E. K.; Truong, K. T.; Dill, K. A.; Cohen, F. E.; Zuckermann, R. N. *PNAS* **1998**, *95*, 4303. (b) Armand, P.; Kirshenbaum, K.; Goldsmith, R. A.; Farr-Jones, S.; Barron, A. E.; Truong, K. T.; Dill, K. A.; Mierke, D. F.; Cohen, F. E.; Zuckermann, R. N.; Bradley, E. K. *PNAS* **1998**, *95*, 4309. (c) Jiang, H.; Léger, J.-M.; Huc, I. *J. Am. Chem. Soc.* **2003**, *125*, 3448.

(7) Corbin, P. S.; Zimmerman, S. C.; Thiessen, P. A.; Hawryluk, N. A.; Murray, T. J. *J. Am. Chem. Soc.* **2001**, *123*, 10475.

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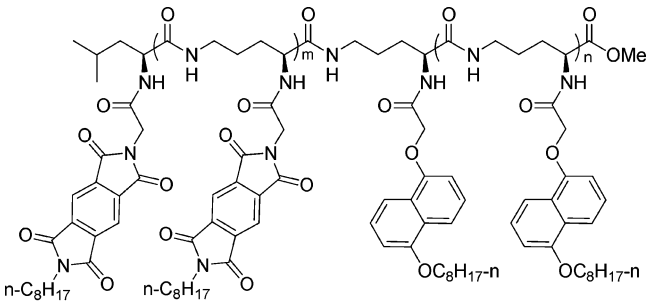
Donor−acceptor interaction is one of the most important noncovalent tools in molecular recognition and self-assembly.[9] Although the stackings between electron-rich aromatic crown ethers and electron-deficient bipyridinium derivatives have played a landmark role in this field,[9] in recent years structurally discrete folded "aedamers",[10] [2]catenanes,[11] [2]rotaxanes and pseudo[2]-rotaxanes,[12] and artificial duplexes[13] have been reported by making use of donor−acceptor interactions between electron-rich 1,5-dialkoxynaphthalene (DAN) or 1,4-dialkoxybenzene units and neutral electron-deficient pyromellitic diimide (PDI) or 1,4,5,8-naphthalene-tetracarboxylic diimide (NDI) units. The very unique feature of the cooperative multisite interaction between the neutral donor and acceptor units exhibited in the new duplexes suggested that this new class of noncovalent interaction might be utilized to control the conformation of large flexible unnatural molecules or molecular systems. In this paper, we report the design, synthesis, and characterization of a new kind of zipper-featured L-ornithine *δ*-peptide foldamers, which are stabilized by the multisite donor−acceptor interactions between the DAN and PDI units.

Results and Discussion

Seven L-ornithine *δ*-peptides **1a**−**g** have been designed and synthesized. The general consideration was to incorporate electron-deficient PDI units and electron-rich DAN units on the carboxyl acid end and the amino end of L-ornithine-derived *δ*-peptides, respectively. In principle, such arrangement of donor and acceptor units would enable adjacent aromatic units in all the *δ*-peptides to possess comparable spatial separation. Cooperative donor−acceptor interactions between the DAN and PDI units in a way reminiscent of one's fingers crossing were expected, which would lead to the formation of a folded conformation for the *δ*-peptide skeletons as shown in Figure 1. The length of the aliphatic chain connecting two adjacent aromatic units is also comparable to that of the tetraoxyethylene chain in Stoddart's aromatic crown ethers, which has been shown to be optimal for efficient intermolecular donor−acceptor interactions.[9] The octyl group is introduced to every aromatic moiety to provide solubility in organic solvents.



1a: m = n = 0 **1e**: m = 2, n = 1
1b: m = 1, n = 0 **1f**: m = 1, n = 2
1c: m = 0, n = 1 **1g**: m = n = 2
1d: m = n = 1

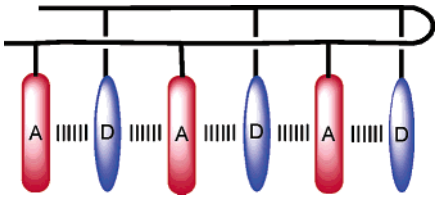


FIGURE 1. Designed zipper-featured folding motif of *δ*-peptides driven by the cooperative donor−acceptor interaction.

δ-Peptides **1a**−**g** have been prepared by the standard liquid-phase method, and were mainly involved in the preparation of two series of key intermediates **5a**−**c** and **10a**−**c** incorporating one to three DAN or PDI units, respectively. The preparations of **5a**−**c** are outlined in Scheme 1. Briefly, Treatment of amine **2** with acid **3** in the presence of DCC afforded compound **4** in 87% yield. Amine **5a** and acid **6** were then obtained in 97% and 92% yields, respectively, upon hydrogenation or hydrolysis of **4**. Amine **5a** reacted with acid **6** in the presence of EDCI to give dipeptide **7**, which was deprotected to afford dipeptide **5b** in 86% yield (two steps). Tripeptide **5c** was then prepared in 68% yield (two steps) from the coupling reaction of **5b** with **6** followed by Pd-catalyzed hydrogenation. All three amines **5a**−**c** were obtained as hydrochloride salts, since the neutral amines were found unstable, and underwent intramolecular nucleophilic substitution to give lactams.[14]

The synthesis of intermediates **10a**−**c** is presented in Scheme 2. L-Leucine was used as the end amino acid of the peptide skeletons for the convenience of synthesis. Since the PDI imide groups were found to be unstable under the reaction conditions to hydrolyze the methyl ester of amino acid derivatives in the presence of lithium hydroxide or other inorganic base, the acid group of

(8) Several rigid glyco- or alkene-based *δ*-peptide analogues with ordered conformations in solution have been reported, see: (a) Machetti, F.; Ferrali, A.; Menchi, G.; Occhiato, E. G.; Guarna, A. *Org. Lett.* **2000**, *2*, 3987. (b) Gardner, R. R.; Liang, G.-B.; Gellman, S. H. *J. Am. Chem. Soc.* **1999**, *121*, 1806. (c) Wipf, P.; Henninger, T. C.; Geib, S. J. *J. Org. Chem.* **1998**, *63*, 6088. (d) von Rödern, E. G.; Lohof, E.; Hessler, G.; Hoffmann, M.; Kessler, H. *J. Am. Chem. Soc.* **1996**, *118*, 10156. (e) Jiang, H.; Léger, J.-M.; Huc, I. *J. Am. Chem. Soc.* **2003**, *125*, 3448. Nowick has recently used ornithine as a scaffold to build hydrogen bond-mediated folding systems, see: Nowick, J. S.; Brower, J. O. *J. Am. Chem. Soc.* **2003**, *125*, 876.

(9) (a) Amabilino D. B.; Stoddart, J. F. *Chem. Rev.* **1995**, *95*, 2725. (b) Philp, D.; Stoddart, J. F. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1154. (c) Fyfe, M. C. T.; Stoddart, J. S. *Acc. Chem. Res.* **1997**, *30*, 393. (d) Raymo, F. M.; Stoddart, J. F. *Chem. Rev.* **1999**, *99*, 1643.

(10) (a) Lokey, R. S.; Iverson, B. L. *Nature* **1995**, *375*, 303. (b) Nguyen, J. Q.; Iverson, B. L. *J. Am. Chem. Soc.* **1999**, *121*, 2639. (c) Zych, A. J.; Iverson, B. L. *J. Am. Chem. Soc.* **2000**, *122*, 8898. (d) Cubberley, M. S.; Iverson, B. L. *J. Am. Chem. Soc.* **2001**, *123*, 7560.

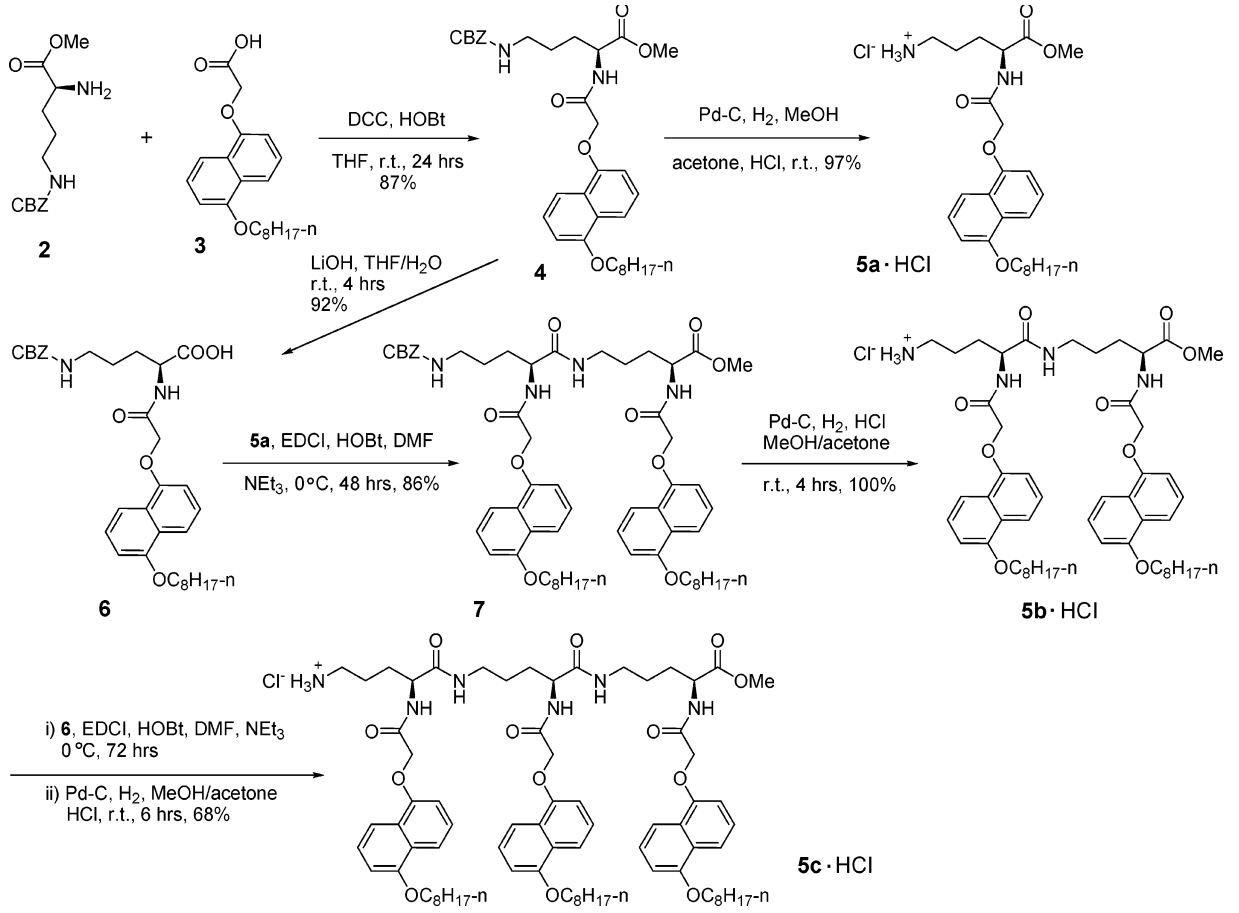
(11) (a) Hamilton, D. G.; Feeder, N.; Prodi, L.; Teat, S. J.; Clegg, W.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1998**, *120*, 1096. (b) Hamilton, D. G.; Davies, J. E.; Prodi, L.; Sanders, J. K. M. *Chem. Eur. J.* **1998**, *4*, 608. (c) Zhang, Q.; Hamilton, D. G.; Feeder, N.; Teat, S. J.; Goodman, J. M.; Sanders, J. K. M. *New J. Chem.* **1999**, *23*, 897. (d) Hansen, J. G.; Feeder, N.; Hamilton, D. G.; Gunter, M. J.; Becher, J.; Sanders, J. K. M. *Org. Lett.* **2000**, *2*, 449.

(12) (a) Gunter, M. J.; Bampos, N.; Johnstone, K. D.; Sanders, J. K. M. *New J. Chem.* **2001**, *25*, 166. (b) Wang, X.-Z.; Li, X.-Q.; Chen, Y.-Q.; Shao, X.-B.; Zhao, X.; Deng, P.; Jiang, X.-K.; Li, Z.-T. *Chem. Eur. J.* **2003**, *9*, 2904. (c) Shao, X.-B.; Jiang, X.-K.; Wang, X.-Z.; Li, Z.-T.; Zhu, S.-Z. *Tetrahedron* **2003**, *59*, 4881.

(13) (a) Gabriel, G. J.; Iverson, B. L. *J. Am. Chem. Soc.* **2002**, *124*, 15174. (b) Zhou, Q.-Z.; Jiang, X.-K.; Shao, X.-B.; Chen, G.-J.; Jia, M.-X.; Li, Z.-T. *Org. Lett.* **2003**, *5*, 1955.

(14) (a) Oklobdzija, M.; Comisso, G.; Decorte, E.; Fajdiga, T.; Gratton, G.; Moimas, F.; Toso, R.; Sunjic, V. *J. Heterocycl. Chem.* **1983**, *20*, 1329. (b) Patterson, K. H.; Depree, G. J.; Zender, J. A.; Morris, Pe. J. *Tetrahedron Lett.* **1994**, *35*, 281.

SCHEME 1



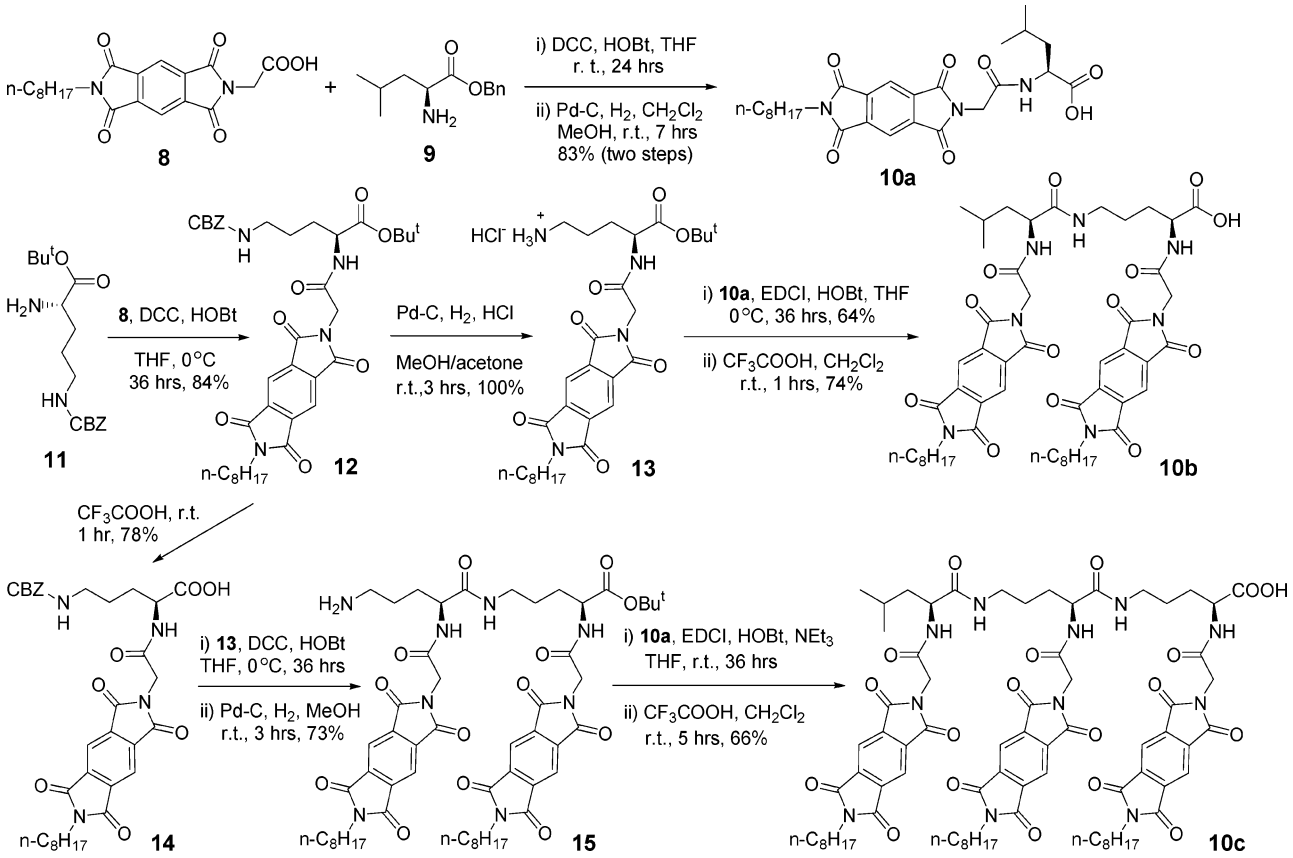
L-ornithine was protected with a *tert*-butyl group, which could be conveniently deprotected with trifluoroacetic acid. Treatment of **10a**−**c** with **5a**−**c** in DMF with EDCI as coupling reagent afforded the target δ-peptides **1a**−**g** in 31−55% yields (Scheme 3). δ-Peptides **1a**−**g** have been characterized by ^{1}H NMR, mass spectroscopy, elemental analysis, and HPLC (>98%). All the oligomers **1a**−**g** are orange solids and their solutions in dichloromethane, chloroform, DMF, or DMSO have pale to dark orange color, depending on their concentrations and lengths.

^{1}H NMR spectra provide the initial evidence that these δ-peptides adopt folded conformations. Sharp peaks were observed for the PDI protons of most of the δ-peptides in DMSO-d_6 (Figure 2). Due to increased overlap, the ^{1}H NMR of long peptides **1f** and **1g** exhibited only one sharp PDI signal, respectively.[15] It can be seen that important upfield shifts were revealed for all these PDI peaks of the δ-peptides compared to that of simple amino acid **10a**. The chemical shifts were essentially concentration independent within the concentration range from 0.2 mM to 0.04 M, ruling out the possibility of important intermolecular interaction. Variable-temperature ^{1}H NMR study also revealed that the chemical shifts of these peptides exhibited very small temperature dependence. For example, increasing the temperature of the solution of **1c** (10 mM) in DMSO-d_6 from 25 °C to 90 °C led to only ca. 0.06 ppm of upfield movement for the PDI proton signals. Moreover, ^{1}H NMR spectra of all the peptide intermediates incorporating two or three PDI units did not exhibit pronounced upfield shifts for the PDI signals in DMSO-d_6. All these observations supported that intramolecular π-stacking occurred as a result of donor−acceptor interaction between the DAN and PDI units. Compared to that of **10a** in $CDCl_3$, substantial upfield shifts were also observed for the PDI protons of peptides **1a** ($\Delta\delta$ −0.34 ppm), **1b** ($\Delta\delta$ −0.26, −0.29 ppm), and **1c** ($\Delta\delta$ −0.52 ppm) in $CDCl_3$. The chemical shifts were also concentration independent, indicating that the upfield shifts were also produced by intramolecular donor−acceptor interaction between the DAN and PDI units. The PDI signals could not be assigned in the ^{1}H NMR spectra of longer peptides **1d**−**g** because of important overlap, implying that stronger π-stackings were also produced in these peptides as a result of increased donor−acceptor interaction.

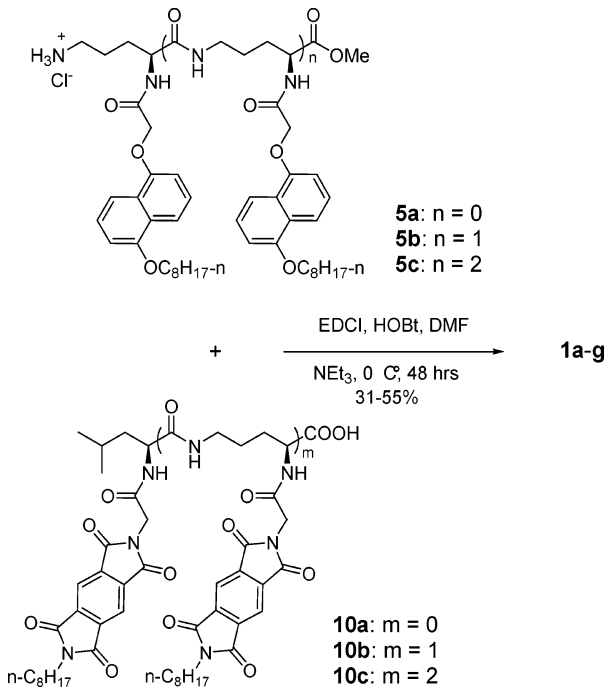
2D-NOESY experiments were also performed to investigate the intramolecular donor−acceptor interaction of the new δ-peptides. Moderate intensity of NOEs was observed between one (8.07 ppm) of the PDI signals and those of the ortho and para protons (6.90, 7.60 ppm) of the DAN units and also the DAN-connected CH_2CO protons (4.71 ppm) in tetrapeptide **1d** in DMSO-d_6 (10 mM) as shown in Figure 3. No obvious connections were displayed between the PDI signals and the meta protons (7.30 ppm) of the DAN units. These observations imply that the adjacent DAN and PDI units stacked with a relative orientation in which the PDI protons were close

(15) Extensive intramolecular aromatic stackings usually lead to lowered resolution of the ^{1}H NMR spectra of folding systems. For examples, see ref 10a and also: Nelson, J. C.; Saven, J. G.; Moore, J. S.; Wolynes, P. G. *Science* **1997**, *277*, 1793.

SCHEME 2



SCHEME 3



to or above the alkoxyl groups of the DAN units. This is consistent with the minimized conformations of δ-peptide **1g** (Figure 10, vide infra). Since no similar NOE connections were observed for all three shorter peptides **1a**−**c** even at higher concentrations (30 mM) in the same solvent,[16] these NOE observations obviously could not be ascribed to the electrostatic interaction between the two neighboring PDI and DAN units in a simple, flexible conformation, but should more reasonably be attributed to a more compact, folded state. NOESY investigations were also performed for the longer δ-peptides **1e**−**g**, which did not provide useful information due to the lowered resolution of their ^{1}H NMR spectra.

UV−vis spectral study provides further strong evidence for the conformational ordering of the δ-peptides. Significant hypochromism and shape differences were observed in the ultraviolet absorption bands of all the peptides **1a**−**g**,[17] compared to that of the 1:1 mixture solution of **5a** and **10a**, when all the UV−vis spectra were recorded at the identical chromophore concentrations in chloroform containing 0.5% trifluoroacetic acid.[18] For example, peptides **1a**, **1d**, and **1g**, which possess the same number of DAN and PDI units, exhibited 15%, 21%, and 28% hypochromism at 298 nm, and 16%, 18%, and 21% hypochromism at 325 nm, respectively (Figure 4).[19,20] It has been well-established that hypochromic effects are dependent on the distance *r* between chromophores as a function of both $1/r^3$ and their relative orientations.[17]

(16) These results reasonably reflect that the donor−acceptor interactions in the shorter δ-peptides are not strong enough to lead to observable NOEs between the DAN and PDI protons, but should not be used to negate the folded conformations of the peptides.

(17) Cantor, C. R.; Schimmel, P. R. *Biophysical Chemistry*; Freeman: New York, 1980.

(18) It was found that the solubility of the long δ-peptides could be improved substantially in chloroform in the presence of even 0.5% of trifluoroacetic acid.

(19) The UV−vis spectra of **1b**, **1c**, **1e**, and **1f** are substantially different in shape due to their varying ratios of DAN and PDI units. However, important hypochromic effects were also exhibited for these δ-peptides.

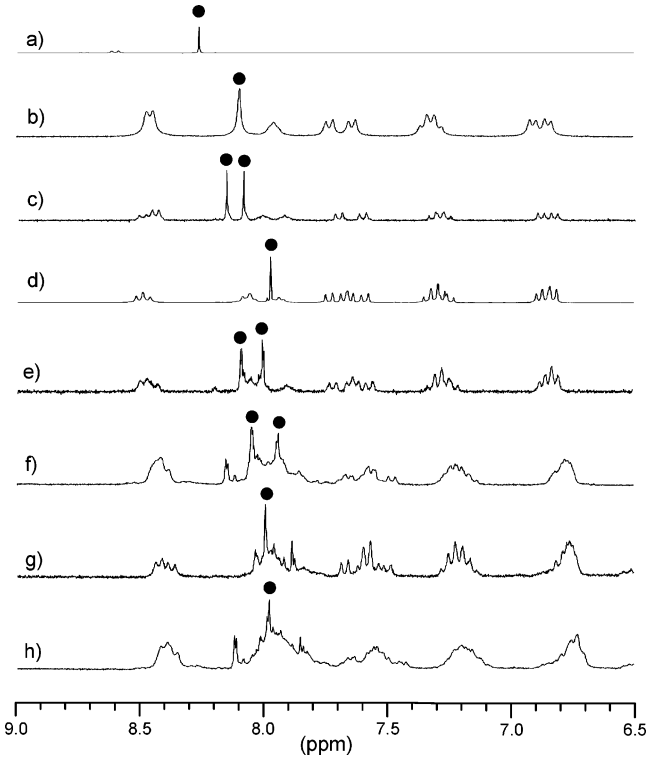


FIGURE 2. Partial ^{1}H NMR spectra (400 MHz) of (a) **10a**, (b) **1a**, (c) **1b**, (d) **1c**, (e) **1d**, (f) **1e**, (g) **1f**, and (h) **1g** in DMSO-d_6 (5 mM) at 25 °C, showing the upfield movement of the chemical shifts of the PDI signals.

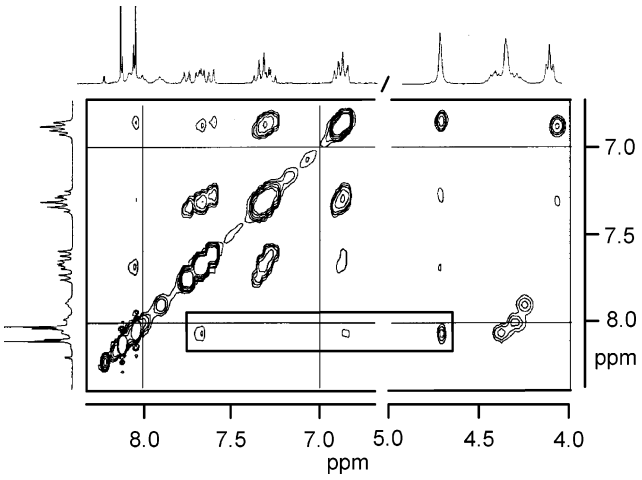


FIGURE 3. Partial NOESY spectrum of tetrapeptide **1d** (10 mM) in DMSO-d_6 at 25 °C, the NOEs exhibited between the signals of the PDI and DAN units highlighting a compact conformation.

Since Beer's law behavior was always observed within the range of concentrations for all the δ-peptides, and the 1:1 solution of **5c** and **10c** in the same solvent also exhibited a comparable hypochromic effect as that of the above **5a** and **10a** system when the spectrum was recorded at the identical chromophore concentration, the possibility that the above hypochromism was generated by intermolecular donor−acceptor interaction could be rule out. It is reasonable to assume that effects due to the peptide backbone and the aliphatic chains are negligible, therefore the hypochromic effect observed for these δ-peptides is obviously generated as a result of the intramolecular donor−acceptor interaction in folded conformations. The increased hypochromism observed for the longer peptides should correspond to more compact, folded states as a result of strengthened donor−acceptor interaction.

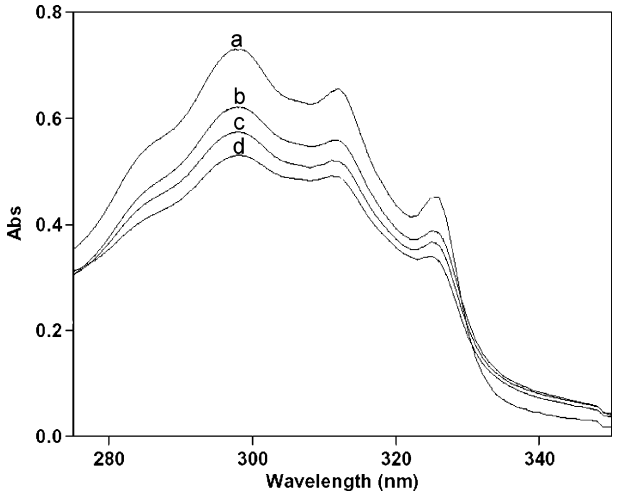


FIGURE 4. Representative UV spectra at [DAN] = [PDI] = 6.0×10^{-5} M in chloroform of 0.5% CF_3COOH at 25 °C, illustrating the hypochromic effect of the folded δ-peptides: (a) **5a** + **10a** (1:1), (b) **1a**, (c) **1d**, and (d) **1g**.

Broad electron-transfer absorbance within the area from 400 to 470 cm^{-1} was observed in the visible spectrum of all the δ-peptides in both organic and aqueous solvents. The molar extinction coefficients (ϵ) at their respective λ_{max} ranging from 421 to 445 cm^{-1} were increased remarkably with the increasing peptide length. In principle, up to $n - 1$ (n represents the peptide length), i.e., one to five independent donor−acceptor interactions, could be formed for δ-peptides **1a**, **1b** and **1c**, **1d**, **1e** and **1f**, and **1g**, respectively. If we assume that all the discrete interactions are comparable in intensity regardless of their relative orientation in the folded conformations, an investigation of the change of the $\epsilon/n - 1$ values, i.e., the average contribution of one donor−acceptor interaction, with $n - 1$ would demonstrate if cooperative effect exists for the donor−acceptor interactions. As can be found in Figure 5, the $\epsilon/n - 1$ values were increased remarkably with the lengthening of δ-peptides in all three solvent systems. Therefore, the donor−acceptor interaction in the δ-peptides should be of cooperativity. Figure 5 also reveals that the charge-transfer absorbance is always notably weaker in chloroform than those in polar DMSO solvents for all the peptides. This observation appears to indicate that besides donor−acceptor interaction, solvophobic interaction might play a more important role in the polar DMSO solvents. It was reported that the stacking interaction between DAN and another neutral electron acceptor, 1,4,5,8-naphthalenetetracarboxylicdiimide, is weakened more substantially in organic solvents of low polarity, relative to that in highly polar or aqueous media, in which hydrophobic interaction contributed

(20) Both DAN and PDI units contribute to these absorbance bands. The data correspond to $(A_0 - A)/A_0$, where A is the combined absorbance of peptide **1**, and A_0 is the combined absorbance of the mixture solution of **5a** and **10a** at the assigned wavelength.

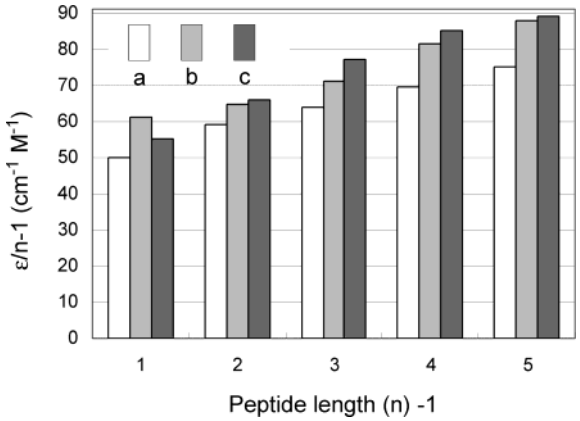


FIGURE 5. The plot of $\epsilon/n - 1$ versus $n - 1$, highlighting the cooperative donor−acceptor interaction in the folded δ-peptides. The ϵ values were measured at 2.0×10^{-3} M at 25 °C in (a) chloroform of 0.5% CF_3COOH, (b) DMF, and (c) DMF−H_2O (95:5).[21] The data for $n - 1 = 2$ and 4 were the average values of tripeptides **1b** and **1c** and pentapeptides **1e** and **1f**, respectively.

more importantly to drive the aromatic stacking.[10d] The present results show that the donor−acceptor interaction between the DAN and PDI units of the new δ-peptides should contribute more importantly to inducing the folding conformation of the δ-peptides and the folding conformations become increasingly compact with the increase of the peptide lengths.

Different from the rigid hydrophobic interaction-driven oligo(phenyleacetylene) folding systems which displayed an obvious threshold number of repeated residues,[15] all the present flexible peptides (even **1a**, which contains only one DAN and one PDI unit) adopt folding conformations. This result reflects the fact that there exists important donor−acceptor interaction even between the single electron-rich and electron-deficient units of the short peptide, as revealed previously in a related report.[12c]

As expected, the donor−acceptor interaction increased at lowered temperature, giving rise to stronger charge-transfer absorption bands. For example, the ϵ value of **1d** in chloroform (1.0 mM) was changed from 210 M^{-1} cm^{-1} at 25 °C to 320 M^{-1} cm^{-1} at 5 °C, indicating a strengthened folding state at reduced temperature. At higher temperature the charge-transfer absorbance became weakened. For example, the ϵ value of **1g** in DMF was reduced from 390 M^{-1} cm^{-1} at 25 °C to 300 M^{-1} cm^{-1} at 50 °C and 150 M^{-1} cm^{-1} at 80 °C, suggesting a less compact folding conformation. The orange color of the solution of **1g** in DMF did not vanish even at 150 °C, indicating that considerably strong intramolecular donor−acceptor interactions still remain. With the decrease of temperature, the orange color of the solution deepened again.[22]

A fluorescent quenching study in chloroform of 0.5% trifluoroacetic acid also supports the folded conformations for the δ-peptides. The relative emission intensity I/I_0 (I = the intensity of the δ-peptides, I_0 = the intensity of **4**,

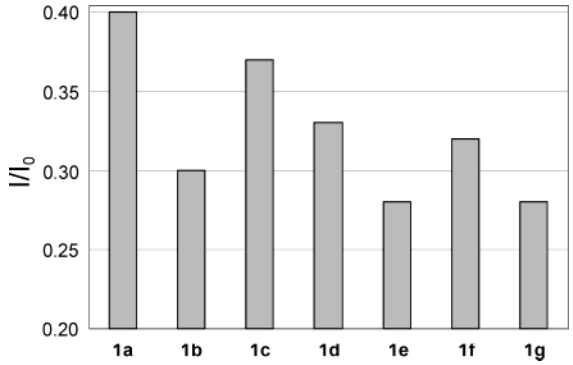


FIGURE 6. Summary of the relative DAN emission intensity of δ-peptides **1a**−**g** (I/I_0) compared to compound **4**, at [DAN] = 6.0×10^{-5} M in chloroform containing 0.5% (v/v) of trifluoroacetic acid at 25 °C, highlighting the increased quenching efficiency of longer δ-peptides.

λ_{max} = 345 cm^{-1}, λ_{ex} = 296 cm^{-1}) of δ-peptides **1a**−**g** at the same [DAN] (6.0×10^{-5} M) is presented in Figure 6. It can be seen that the fluorescence of the DAN unit of all the δ-peptides was substantially quenched and the quenching became increasingly efficient as the δ-peptide length was increased by comparing the data of **1a**, **1d**, and **1g**, which possess the same number of DAN and PDI units, respectively.[23] These results are also consistent with the opinion that the folded conformations became more compact in the longer δ-peptides as a result of strengthened intramolecular donor−acceptor interaction. The remarkably more efficient quenching result exhibited from **1b** and **1e** relative to that of their adjacent peptides could be rationalized by considering the fact that these two compounds possess the highest ratios of PDI unit over DAN unit, which facilitated the energy transfer of the excited DAN to the PDI units. At reduced temperature, the quenching becomes more efficient. For example, the I/I_0 value of **1d** and **1g** in chlorofrom (with 0.5% CF_3COOH) was reduced from 0.33 and 0.28 to 0.24 and 0.17, respectively, when the temperature was reduced from 25 °C to 5 °C. This observation also supports the folding comformation becoming more compact at low temperature.

Circular dichroism (CD) spectroscopy has been widely applied for investigation of compact conformation of discrete foldamers.[1b,c,g,h] To establish if δ-peptides **1a**−**g** possessed a common folding module, CD measurements were also performed in chloroform with 0.5% of CF_3-$COOH$. It was found that the solutions of all the chiral compounds **4**, **5a**−**c**, **10a**−**c**, and **12** or the 1:1 mixture solutions (6.0×10^{-4} M) of **5** and **10** with the same number of aromatic units in the same solvent system exhibited no measurable ellipticity within the range of 260−400 nm, indicating that all the compounds were in a random, flexible conformation. In contrast, remarkable positive Cotton effects, with a similar spectral shape, were observed for the δ-peptides, as shown in Figure 7. It can be seen that the intensities of the CD bands are

(21) Because of the rapidly reduced solubility of longer δ-peptides, the absorption spectra of the peptides could be obtained in the DMSO−H_2O systems with higher water content.

(22) Irreversible unfolding or denaturation of ionic peptide aedamers has been reported, see ref 10b.

(23) The DAN fluorescent intensity of a mixture solution of **4** and **12** (1:1, 6.0×10^{-5} M) in chloroform containing 0.5% of CF_3COOH is ca. 92% of that of a chloroform solution of **4** at the same concentration. Therefore, the fluorescent quenching observed for the peptides is obviously mainly due to intramolecular interactions between DAN and PDI units.

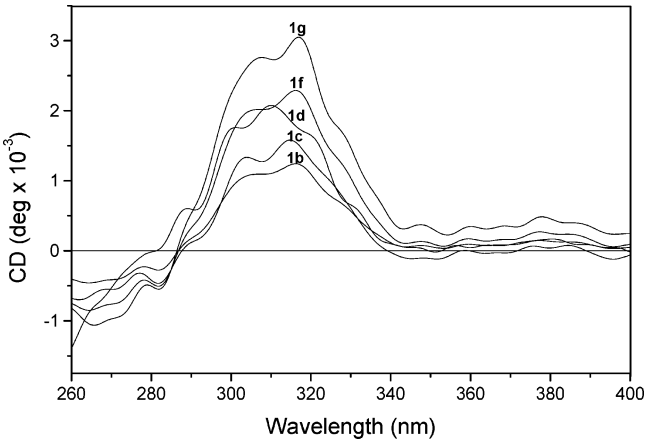


FIGURE 7. Representative CD spectra of δ-peptides, recorded at [DAN] = 6.0×10^{-4} M for all samples in chloroform containing 0.5% of CF_3COOH at 25 °C.

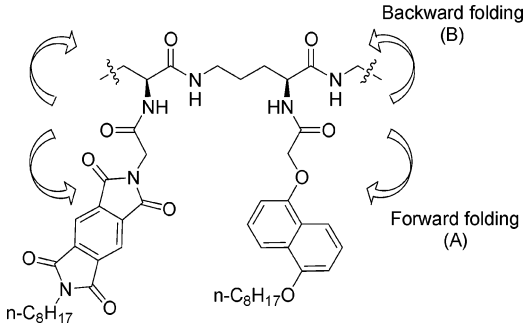


FIGURE 8. Two possible folding patterns of the chiral δ-peptide backbone.

increased pronouncedly with the increase of the δ-peptide chain length. In addition, the intensities of all the peptides were found to be linearly dependent on their concentrations within the concentration range from 5.0×10^{-5} to 5.0×10^{-3} M. These observations also supported the δ-peptides adopting folding patterns, as shown in Figure 1, although the exact folding conformation could not be determined.

A CPK modeling study showed that the chiral δ-peptide skeletons of **1a**−**g** might adopt two major folding patterns for achieving efficient crossing arrangement of the donor and acceptor units, as shown in Figure 8. For peptides **1b**, **1c**, **1e**, and **1f**, without considering the folding patterns of the skeletons, there exists only one mode of crossing arrangement of the aromatic units by which the maximum number of donor−acceptor interacting sites can be achieved. In contrast, for δ-peptides such as **1d** and **1g**, both of which are incorporated with the same number of DAN and PDI units, respectively, there are two different orientation patterns, i.e., I and II as shown in Figure 9, both of which could provide the utmost of five donor−acceptor interacting sites. Therefore, if we assume that the conformations possessing the maximum number of donor−acceptor interacting sites are most stable for all the δ-peptides, there should be two major low-energy folding states for **1b**, **1c**, **1e**, and **1f** and four major low-energy folding states for **1d** and **1g**, respectively. Since numerous attempts to crystallize **1** were unsuccessful, both molecular mechanic and quantum

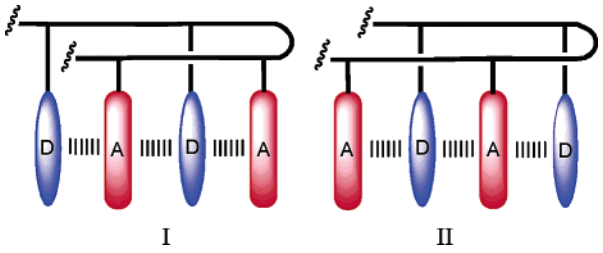


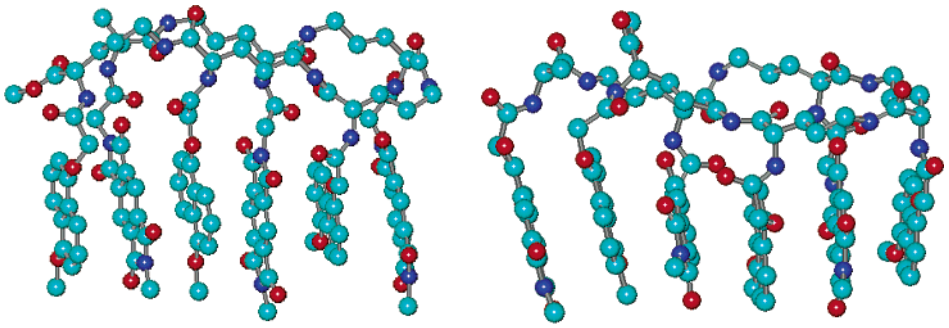
FIGURE 9. Two low-energy arranging modes of DAN and PDI units in folded δ-peptides **1d** and **1g** with the same number of DAN and PDI units.

mechanic calculations were carried out for the longest δ-peptide **1g** to obtain more insight for the structures of the most stable folding conformations. It was found that the two low-energy conformations generated from pattern B in Figure 8 are notably of higher energy than the two conformations (vide infra, Figure 10) formed from pattern A as shown in Figure 8. Figure 10 provides the minimized structures (A and B) of the 2-folding conformations, which have been obtained by using the conjugate gradient method with the AMBER force field.[24] Calculation with density function B3LYP/6-31g with an Onsager model in DMSO shows that conformation A is more stable than conformation B (Figure 10) with an energy difference of 26.80 kcal/mol.[25,26] A molecular modeling study also revealed that the stacking DAN and PDI aromatics of the δ-peptides are not arranged in a "perfect" face-to-face manner in the folded states, which might reflect the feature of nondirectionality of this kind of donor−acceptor interaction. The calculation also showed that the distances between the adjacent DAN and PDI units for conformation A and conformation B are about 3.3−3.6 Å.[27] The face-to-face manner in the folded states is better for conformation A than conformation B.

Conclusions

We have described a general strategy for creating the first-generation of L-ornithine-based δ-peptide foldamers, whose ordered conformations are stabilized by cooperative donor−acceptor interaction between 1,5-dialkoxynaphthalene (DAN) and pyromellitic diimide (PDI) units. A noticeable feature of these zipper-featured foldamers is that their folding conformations are stable in both nonpolar and polar solvents. In principle, the structure of the peptide backbones should tolerate many modifications and the DAN−PDI interaction moiety might be replaced with chemically and photochemically active donor−acceptor systems, which would lead to controllable and functionalized folding architectures. A combinatorial library of even longer δ-peptide oligomers might also be

(24) Weiner, S. J.; Kollman, P. A.; Case, D. A.; Singh, U. C.; Ghio, C.; Alagona, G.; Profeta, J. S.; Weiner, P. *J. Am. Chem. Soc.* **1984**, *106*, 765−784.
(25) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.
(26) (a) Ditchfield, R.; Hehre, W. J.; Pople, J. A. *J. Chem. Phys.* **1971**, *54*, 724. (b) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257. (c) Hariharan, P. C.; Pople, J. A. *Mol. Phys.* **1974**, *27*, 209. (d) Wong, M. W.; Wiberg, K. B.; Frisch, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 1645.
(27) Anelli, P. L.; Ashton, P. R.; Ballardini, R.; Balzani, V.; Delgado, M.; Gandolfi, M. T.; Goodnow, T. T.; Kaifer, A. E.; Philp, D.; Pietraszkiewicz, M.; Prodi, L.; Reddington, M. V.; Slawin, A. M. Z.; Spencer, N.; Stoddart, J. F.; Vicent, C.; Williams, D. J. *J. Am. Chem. Soc.* **1992**, *114*, 193.



A B

FIGURE 10. Two minimized structures of δ-peptide **1g**, with different arranging patterns of the DAN and PDI units. The peptide backbone adopts the forward folding motif (pattern A) as shown in Figure 8.

constructed by making use of the solid-phase synthetic technique, which might provide new platforms for developing new abiotic molecules with tertiary structures.

Experimental Section

General. See the Supporting Information.

Compound 3. To a stirred solution of 1,5-dihydroxynaphthalene (6.40 g, 40.0 mmol) in acetone (150 mL) were added potassium carbonate (12.0 g, 87.0 mmol), potassium iodide (6.64 g, 40 mmol), and *n*-octyl bromide (7.0 mL, 40.0 mmol). The suspension was heated under reflux for 10 h and then cooled to room temperature. The solid was filtered off and the solvent was removed under reduced pressure. The resulting residue was triturated with ethyl acetate (100 mL) and the organic phase washed with aqueous hydrochloride solution (20 mL), water (20 mL), and brine (20 mL) and dried over Na_2SO_4. After removal of the solvent in vacuo, the crude product was purified by column chromatography (petroleum ether/AcOEt 5:1), to give 5-octyloxynaphthalen-1-ol as a white solid (2.40 g, 22%). Mp 78−80 °C. ^{1}H NMR ($CDCl_3$) δ 7.88 (d, J = 8.5 Hz,1 H), 7.11 (d, J = 8.5 Hz, 1H), 7.37 (t, J = 8.3 Hz,1 H), 7.28 (t, J = 8.3 Hz,1 H), 6.84 (d, J = 7.4 Hz, 1 H), 6.82 (d, J = 7.6 Hz, 1 H), 5.29 (s, 1 H), 4.12 (t, J = 6.4 Hz, 2 H), 2.18−1.87 (m, 2 H), 1.58−1.51 (m, 2 H), 1.42−1.30 (m, 8 H), 0.91−0.87 (m, 3 H). MS (EI) *m*/*z* 272 [M^+]. Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79.36; H, 8.90. Found: C, 79.38; H, 8.92. To a stirred solution of the above 5-octoxy-1-naphthalenol (2.10 g, 7.70 mmol) in acetone (80 mL) was added sodium hydroxide (0.36 g, 9.00 mmol). After the solution was stirred for 0.5 h, ethyl bromoacetate (0.90 mL, 8.00 mmol) was added dropwise and the suspension was heated under reflux for 10 h. Upon cooling to room temperature, aqueous NaOH solution (1 N, 10 mL) was added and the mixture was stirred for 2 h. Dilute hydrochloric acid was then added to pH 4 and the mixture was concentrated under reduced pressure to ca. 30 mL. The resulting precipitate was filtered, washed with water thoroughly, and recrystallized from acetone to afford compound **3** as a white solid (2.00 g, 78%). Mp 171−172 °C. ^{1}H NMR (DMSO-d_6) δ 13.07 (s, 1 H), 7.75 (t, J = 7.5 Hz, 2 H), 7.42−7.34 (m, 2 H), 6.98 (d, J = 7.5 Hz, 1 H), 6.89 (d, J = 7.8 Hz, 1 H), 4.86 (s, 2 H), 4.12 (t, J = 6.3 Hz, 2 H), 1.88−1.79 (m, 2 H), 1.51−1.27 (m, 10 H), 0.86 (t, J = 6.3 Hz, 3 H). MS (EI) *m*/*z* 330 [M^+]. Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.69, H, 7.95. Found: C, 72.66; H, 7.72.

Compound 4. To a stirred solution of amine **2**[28] (1.58 g, 5.00 mmol) in dichloromethane cooled in an ice bath were added *N*-methylmorpholine (0.55 mL, 5.00 mmol) and acid **3** (1.65 g, 5.00 mmol), *N*-hydroxybenzotrizole (HOBt) (0.68 g, 5.00 mmol), and DCC (1.03 g, 5.00 mmol). The mixture was stirred at 0 °C for 2 h and then at room temperature for 12 h. The resulting solid was filtered off and the filtrate concentrated in vacuo to give a residue, which was triturated in ethyl acetate (70 mL). The organic solution was washed with 1% aqueous hydrochloric acid (30 mL), water (2 × 30 mL), and brine (30 mL), and dried over Na_2SO_4. Upon removal of the solvent in vacuo, the resulting residue was subjected to column chromatography (CH_2Cl_2/EtOH 20:1) to afford compound **4** as a white solid (2.57 g, 87%). Mp 100−101.5 °C. $[\alpha]^{20}_D$ 3.49 (*c* 1.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.96 (d, J = 8.4 Hz, 1 H), 7.80 (d, J = 8.4 Hz, 1 H), 7.44 (t, J = 8.4 Hz, 1 H), 7.38−7.28 (m, 7 H), 6.84 (t, J = 8.4 Hz, 2 H), 5.05 (s, 2 H), 4.86 (s, br, 1 H), 4.75−4.64 (m, 3 H), 4.11 (t, J = 6.3 Hz, 2 H), 3.74 (s, 3 H), 3.15 (d, J = 6.3 Hz, 2 H), 1.91 (m, 4 H), 1.72−1.30 (m, 12 H), 0.90 (t, J = 6.6 Hz, 3 H). MS (EI) *m*/*z* 592 [M^+]. Anal. Calcd for $C_{34}H_{44}N_2O_7$: C, 68.89; H, 7.50; N, 4.72. Found: C, 69.05; H, 7.48; N, 4.80.

Compound 5a. To a solution of compound **4** (1.57 g, 2.65 mmol) in acetone/methanol (40 mL/40 mL) were added hydrochloric acid (2 N, 0.5 mL) and Pd/C (10%, 0.16 g). The suspension was stirred at room temperature under 1 atm of hydrogen gas for 5 h. The solid was filtered off and the solution concentrated to give **5a** as a white solid (1.27 g, 97%), which was further purified for microanalysis by recrystallization from dichloromethane. Mp 170−172 °C. $[\alpha]^{20}_D$ −6.88 (*c* 1.25, ethanol). ^{1}H NMR ($CDCl_3$) δ 8.24 (s, br, 3 H), 7.88 (d, J = 8.4 Hz, 1 H), 7.76 (d, J = 8.1 Hz, 1 H), 7.54 (d, J = 7.2 Hz, 1 H), 7.37 (t, J = 7.8 Hz, 1 H), 7.28 (t, J = 8.4 Hz, 1 H), 6.76 (d, J = 7.8 Hz, 2 H), 4.78−4.50 (m, 3 H), 4.02 (t, J = 6.3 Hz, 2 H), 3.70 (s, 3 H), 3.04 (s, br, 2 H), 1.91−1.82 (m, 4 H), 1.54−1.25 (m, 12 H), 0.89 (t, J = 6.6 Hz, 3 H). MS (EI) *m*/*z* 458 [M − HCl]$^+$. Anal. Calcd for $C_{26}H_{38}N_2O_5$·HCl: C, 63.07; H, 7.96; N, 5.66. Found: C, 63.08; H, 7.67; N, 5.60.

Compound 6. A solution of compound **4** (2.50 g, 4.30 mmol) and LiOH·H_2O (0.24 g, 4.30 mmol) in THF (50 mL)−water (2 mL) was stirred at room temperature until **4** was consumed (detected by TLC). The solution was concentrated in vacuo and dilute hydrochloric acid (2 N) was added to pH 3. The resulting precipitate was filtered, washed with water thoroughly, and dried in vacuo to afford compound **6** as a white solid (2.30 g, 92%). Mp 125−126 °C. $[\alpha]^{20}_D$ 4.54 (*c* 1.19, ethanol). ^{1}H NMR (DMSO-d_6) δ 8.37 (d, J = 7.5 Hz, 1 H), 7.82 (d, J = 8.7 Hz, 1 H), 7.75 (d, J = 8.7 Hz, 1 H), 7.43−7.28 (m, 7 H), 6.98 (d, J = 7.8 Hz, 1 H), 6.92 (d, J = 7.8 Hz, 1 H), 5.00 (s, 2 H), 4.73 (s, 2 H), 4.31−4.27 (m, 1 H), 4.12 (t, J = 6.0 Hz, 2 H), 3.00 (t, J = 6.3 Hz, 2 H), 1.86−1.27 (m, 16 H), 0.86 (t, J = 6.9 Hz, 3 H). MS (EI) *m*/*z* 560 [M − H_2O]$^+$. Anal. Calcd for $C_{33}H_{42}N_2O_7$·H_2O: C, 66.41; H, 7.45; N, 4.70. Found: C, 66.59; H, 7.22; N, 4.60.

Compound 7. Acid **6** (1.72 g, 2.97 mmol) and HOBt (0.41 g, 3.00 mmol) were dissolved in dried DMF (20 mL) at 0 °C, then EDCI (0.58 g, 3.00 mmol) was added. After the mixture

(28) Rosowsky, A.; Forsch, R. A.; Bader, H.; Freisheim, J. H. *J. Med. Chem.* **1991**, *34*, 1447.

was stirred for 10 min, a solution of triethylamine (0.42 mL, 2.97 mmol) and **5a** (1.47 g, 2.97 mmol) in DMF (20 mL) was added dropwise. Stirring was continued at 0 °C for 4 h and then at room temperature for 48 h. The solvent was removed under reduced pressure and the resulting residue was triturated with dichloromethane (100 mL). The organic phase was washed base free and dried over Na_2SO_4. After the solvent was removed, the crude product was chromatographed (CH_2Cl_2/MeOH 20:1) to afford **7** as a white solid (2.60 g, 86%). Mp 149−150 °C. $[\alpha]^{20}_D$ 10.4 (*c* 1.03, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.96−7.92 (m, 2 H), 7.82−7.78 (m, 2 H), 7.46−7.38 (m, 4 H), 7.36−7.27 (m, 7 H), 6.85−6.71 (m, 5 H), 5.21 (s, br, 1 H), 5.06 (s, 2 H), 4.67−4.53 (m, 6 H), 4.12−4.07 (m, 4 H), 3.75 (s, 3 H), 3.37−3.30 (m, 2 H), 3.19−3.14 (m, 2 H), 1.95−1.87 (m, 8 H), 1.75−1.26 (m, 24 H), 0.90 (t, J = 6.9 Hz, 6 H). MS (MALDI-tof) *m*/*z* 1041 $[M + Na]^+$. Anal. Calcd for $C_{59}H_{78}N_4O_{11}$: C, 69.51; H, 7.73; N, 5.49. Found: C, 69.35; H, 8.16; N, 5.36.

Compound 5b was prepared quantitatively as a salt of hydrochloric acid from **7** according to the procedure described for **5a**, and used directly for the next steps without further purification.

Compound 5c. A tripeptide was first prepared as a white solid (68%) from the reaction of **5b** and **12** according to the procedure described for preparing compound **7**. Mp 196−198 °C. $[\alpha]^{20}_D$ 9.76 (*c* 0.84, CH_2Cl_2/MeOH 9:1). ^{1}H NMR ($CDCl_3$) δ 7.94−7.90 (m, 3 H), 7.79 (t, J = 8.4 Hz, 3 H), 7.52−7.28 (m, 14 H), 7.02 (br, 2 H), 6.82−6.69 (m, 6 H), 5.24 (s, br, 1 H), 5.04 (s, 2 H), 4.63−4.52 (m, 9 H), 4.10−4.00 (m, 6 H), 3.70 (s, 3 H), 3.47−3.20 (br, 4 H), 1.92−1.26 (m, 48 H), 0.89 (t, J = 6.3 Hz, 9H). MS (MALDI-tof) *m*/*z* 1468 $[M + Na]^+$. Anal. Calcd for $C_{84}H_{112}N_6O_{15}$: C, 69.77; H, 7.82; N, 5.81. Found: C, 69.75; H, 7.73; N, 5.64. **5c** was prepared quantitatively from the peptide according to the procedure described for **5a**, and used directly for the next steps without further purification.

Compound 8. A solution of 1,2,4,5-benzenetetracarboxylic anhydride (13.2 g, 20.0 mmol), glycine (4.50 g, 20.0 mmol), and *n*-octylamine (9.90 mL, 60.0 mmol) in DMF (150 mL) was stirred at 120 °C for 4 h. Upon cooling to room temperature, the resulting solid was filtered off. Water (300 mL) was added to the filtrate and the precipitate formed was filtered, washed with water (30 mL), and then triturated with dichloromethane (20 mL). The solid was filtered again, washed with acetone (20 mL), and dried in vacuo to give **8** as a white solid (3.65 g, 16%). Mp 246−248 °C. ^{1}H NMR (DMSO-d_6) δ 13.39 (s, br, 1 H), 8.27 (s, 2 H), 4.39 (s, 2 H), 3.61 (t, J = 6.9 Hz, 2 H), 1.62 (t, J = 6.0 Hz, 2 H), 1.28−1.24 (m, 10 H), 0.85 (t, J = 6.3 Hz, 3 H). MS (EI) *m*/*z* 386 $[M]^+$. Anal. Calcd for $C_{20}H_{22}N_2O_6$: C, 62.16; H, 5.75; N, 7.25. Found: C, 62.19; H, 5.82; N, 7.12.

Compound 10a. According to the reaction conditions described for the preparation of **4**, acid **8** reacted with amine **9** to afford the corresponding amide as a white solid (84%). Mp 80−82 °C. $[\alpha]^{20}_D$ 1.9 (*c* 0.93, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 8.29 (s, 2 H), 7.39−7.30 (m, 5 H), 6.29 (s, br, 1 H), 5.21 (s, 2 H), 4.73−4.66 (m, 1 H), 4.43 (d, J = 7.8 Hz, 2 H), 3.74 (t, J = 6.6 Hz, 2 H), 1.70−1.54 (m, 5 H), 1.33−1.23 (m, 10 H), 0.93−0.85 (m, 9 H). MS (EI) *m*/*z* 590 $[M + H]^+$. Anal. Calcd for $C_{33}H_{39}N_3O_7$: C, 67.21; H, 6.68; N, 7.13. Found: C, 67.26; H, 6.50; N, 7.05. A solution of the amide (3.60 g, 6.10 mmol) in dichloromethane (30 mL)/methanol (30 mL) was stirred for 7 h at room temperature in the presence of Pd/C (10%, 0.40 g) at 1 atm of hydrogen gas. The catalyst was then filtered off and the solvent removed. The crude product was subjected to flash chromatography (CH_2Cl_2/MeOH 10:1), to give **10a** as a white solid (2.98 g, 98%). Mp 164−166 °C. $[\alpha]^{20}_D$ −2.0 (*c* 0.93, $CHCl_3$). ^{1}H NMR (DMSO-d_6) δ 12.66 (s, 1 H), 8.58 (d, J = 8.1 Hz, 1 H), 8.24 (s, 2 H), 4.30−4.21 (m, 3 H), 3.61 (t, J = 6.3 Hz, 2 H), 1.66−1.50 (m, 5 H), 1.28−1.24 (m, 10 H), 0.91−0.82 (m, 9 H). MS (EI) *m*/*z* 455 $[M - CO_2]^+$. Anal. Calcd for $C_{26}H_{33}N_3O_7$: C, 62.50; H, 6.67; N, 8.41. Found: C, 62.79; H, 6.67; N, 8.39.

Compound 12 was prepared as a white solid (83%) from compounds **8** and **11**[29] according to the procedure described for the preparation of **4**. Mp 98−99 °C. $[\alpha]^{20}_D$ 18.0 (*c* 0.91, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 8.27 (s, 2 H), 7.31−7.28 (m, 5 H), 6.84 (d, J = 7.2 Hz, 1 H), 5.05 (s, br, 3 H), 4.52−4.36 (m, 3 H), 3.73 (t, J = 7.2 Hz, 2 H), 3.22 (s, br, 2 H), 1.69−1.52 (m, 4 H), 1.46 (s, 9 H), 1.33−1.26 (m, 12 H), 0.87 (t, J = 6.3 Hz, 3 H). MS (MALDI-tof) *m*/*z* 713 $[M + Na]^+$. Anal. Calcd for $C_{37}H_{46}N_4O_9$: C, 64.32; H, 6.72; N, 8.11. Found: C, 64.01; H, 6.81; N, 7.98.

Compound 13 was prepared quantitatively from **12** according to the procedure described for **5a**, and used directly for the next step without further purification. This compound is unstable in the air.

Compound 10b. According to the procedure described for the preparation of **4**, **10a** reacted with **13** to afford the corresponding dipeptide in 64% yield. White solid. Mp >213 °C dec. $[\alpha]^{20}_D$ 9.81 (*c* 1.06, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 8.22 (s, 2 H), 8.18 (s, 2 H), 7.72 (d, J = 7.8 Hz, 1 H), 7.13 (s, br, 1 H), 7.11 (s, br, 1 H), 4.57−4.39 (m, 6 H), 3.72 (t, J = 7.2 Hz, 4 H), 3.41 (s, br, 1 H), 3.09 (s, br, 1 H), 1.84−1.59 (m, 11 H), 1.42 (s, 9 H), 1.31−1.25 (m, 20 H), 0.87−0.83 (m, 12 H). MS (MALDI-tof) *m*/*z* 1061 $[M + Na]^+$. Anal. Calcd for $C_{55}H_{71}N_7O_{13}$: C, 63.62; H, 6.91; N, 9.44. Found: C, 63.43; H, 6.81; N, 9.18. A solution of the above peptide (0.50 g, 0.72 mmol) in dichloromethane (10 mL)−trifluoroacetic acid (5 mL) was stirred at room temperature until the starting material was consumed (9 h). The solvent was removed under reduced pressure and the resulting residue was washed acid free with water, dried, and subjected to column chromatography (CH_2Cl_2/MeOH 10:1) to afford **10b** (0.36 g, 74%) as a white solid. Mp 236−238 °C. $[\alpha]^{20}_D$ −7.56 (*c* 0.82, DMF). ^{1}H NMR (DMSO-d_6) δ 8.60 (d, J = 7.8 Hz, 1 H), 8.45 (d, J = 8.4 Hz, 1 H), 8.24 (s, 4 H), 8.00 (t, J = 5.7 Hz, 1 H), 4.35−4.22 (m, 6 H), 3.62 (t, J = 7.2 Hz, 4 H), 3.08 (m, 2 H), 1.73−1.25 (m, 31 H), 0.91−0.84 (m, 12 H). MS (ESI) *m*/*z* 981 $[M]^+$. Anal. Calcd for $C_{51}H_{63}N_7O_{13}$: C, 62.36; H, 6.48; N, 9.98. Found: C, 62.40; H, 6.75; N, 9.54.

Compound 14 was prepared as a white solid (78%) from **12** according to the procedure described for the preparation of **10b**. Mp 146−148 °C. $[\alpha]^{20}_D$ 12.9 (*c* 0.98, $CHCl_3$). ^{1}H NMR (DMSO-d_6) δ 8.61 (t, J = 7.8 Hz, 1 H), 8.24 (s, 2 H), 7.40−7.29 (m, 5 H), 5.00 (s, 2 H), 4.32 (s, 2 H), 4.20 (m, 1 H), 3.61 (t, J = 6.6 Hz, 2 H), 3.00 (s, br, 2 H), 1.80−1.42 (m, 6 H), 1.39−1.24 (m, 10 H), 0.82 (t, J = 6.6 Hz, 3 H). MS (ESI) *m*/*z* 657 $[M + Na]^+$. Anal. Calcd for $C_{33}H_{38}N_4O_9$: C, 62.44; H, 6.05; N, 8.83. Found: C, 62.59; H, 6.01; N, 8.67.

Compound 15. Compound **13** reacted with **14** to afforded the corresponding dipeptide as a white solid (74%) according to the procedure as described for the preparation of **22**. Mp 196 °C dec. $[\alpha]^{20}_D$ 5.0 (*c* 1.08, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 8.24 (s, 4 H), 7.52 (d, J = 7.8 Hz, 1 H), 7.31−7.25 (m, 5 H), 7.06 (d, J = 8.1 Hz, 1 H), 6.84 (t, J = 5.4 Hz, 1 H), 5.26 (t, J = 6.0 Hz, 1 H), 4.95 (s, 2 H), 4.53−4.36 (m, 6 H), 3.71 (t, J = 7.5 Hz, 4 H), 3.34−3.14 (m, 4 H), 1.87 (m, 2 H), 1.74−1.50 (m, 10 H), 1.45 (s, 9 H), 1.32−1.26 (m, 20 H), 0.83 (t, J = 6.6 Hz, 6 H). MS (MALDI-tof) *m*/*z* 1172 $[M]^+$. Anal. Calcd for $C_{62}H_{76}N_8O_{15}$: C, 63.46; H, 6.54; N, 9.55. Found: C, 63.26; H, 6.49; N, 9.37. Compound **15** was prepared quantitatively from the peptide according to the procedure as described for the preparation of compound **10a** and used for the next step without further purification.

Compound 10c. A tripeptide intermediate was first prepared in 66% yield from the reaction of compounds **10a** and **15** according to the procedure described for **7**. Mp 260 °C dec. $[\alpha]^{20}_D$ 10.8 (*c* 0.51, CH_2Cl_2 (10% MeOH)). ^{1}H NMR (DMSO-d_6) δ 8.58−8.42 (m, 3 H), 8.22 (s, 6 H), 8.00 (s, br, 2 H), 4.40−4.05 (m, 9 H), 3.59 (s, br, 6 H), 3.05 (s, br, 4 H), 1.60−1.21 (m, 56 H), 0.73 (m, 15 H). MS (MALDI-tof) *m*/*z* 1519 $[M]^+$, 1544 $[M + Na]^+$. HRMS-MS (MALDI-tof) *m*/*z* 1520.7277. Calcd for $C_{80}H_{101}N_{11}O_{19}$ 1520.7207. The above compound was stirred in dichloromethane/trifluoroacetic acid (2:1) at room temperature

(29) Kempton, R. J.; Black, A. M.; Anstead, G. M.; Kumar, A. A.; Blankenship, D. T.; Freisheim, J. H. *J. Med. Chem.* **1982**, *25*, 475.

until it was consumed. After the solvent was removed, the product **10c** was obtained, which was washed with water and ether thoroughly, dried in vacuo, and used for the next step without further purification.

Dipeptide 1a was prepared in 42% yield as an orange solid from the reaction of **5a** and **10a**, according to the procedure as described for compound **7**. Mp 193−194 °C. $[\alpha]^{20}_D$ 16.1 (*c* 0.93, $CHCl_3$). ^{1}H NMR ($CDCl_3$) *δ* 7.91 (s, 2 H), 7.69 (d, *J* = 8.5 Hz, 1 H), 7.60−7.50 (m, 2 H), 7.30−7.24 (m, 2 H), 6.78 (d, *J* = 7.0 Hz, 1 H), 6.69 (d, *J* = 7.1 Hz, 1 H), 6.50 (s, br, 2 H), 4.74−4.38 (m, 6 H), 4.04 (t, *J* = 6.5 Hz, 2 H), 3.80 (s, 3 H), 3.69 (t, *J* = 7.0, 2 H), 3.50 (s, br, 1 H), 3.15 (s, br, 1 H), 1.92−1.54 (m, 11 H), 1.36−1.26 (m, 20 H), 0.92−0.86 (m, 12 H). MS (ESI) *m*/*z* 963 $[M + Na]^+$. Anal. Calcd for $C_{52}H_{69}N_5O_{11}$: C, 66.42; H, 7.41; N, 7.45. Found: C, 66.81; H, 7.48; N, 7.13.

Tripeptide 1b was prepared in 54% yield as an orange solid, from the reaction of **5a** and **10b**. Mp 234−236 °C. $[\alpha]^{20}_D$ −5.70 (*c* 0.71, $CHCl_3$ (0.5% CF_3COOH)).^{1}H NMR (DMSO-d_6) *δ* 8.52−8.43 (m, 3 H), 8.17 (s, 2 H), 8.10 (s, 2 H), 8.00 (t, *J* = 5.1 Hz, 1 H), 7.92 (t, *J* = 5.8 Hz, 1 H), 7.73 (d, *J* = 8.5 Hz, 1 H), 7.64 (d, *J* = 8.5 Hz, 1 H), 7.36−7.27 (m, 2 H), 6.90 (d, *J* = 7.4 Hz, 1 H), 6.86 (d, *J* = 7.7 Hz, 1 H), 4,71 (s, 2 H), 4.41−4.23 (m, 7 H), 4.09 (t, *J* = 6.3 Hz, 2 H), 3.64 (s, 3 H), 3.59 (t, *J* = 7.2 Hz, 4 H), 3.08−3.04 (m, 4 H), 1.89−1.24 (m, 47 H), 0.89−0.82 (m, 15 H). MS (MALDI-tof) *m*/*z* 1445 $[M + Na]^+$. Anal. Calcd for $C_{77}H_{99}N_9O_{17}$: C, 64.99; H, 7.03; N, 8.86. Found: C, 64.93; H, 7.22; N, 8.67.

Tripeptide 1c. To a stirred solution of **5b** (0.27 g, 0.30 mmol), **10a** (0.15 g, 0.30 mmol), and HOBt (0.054 g, 0.40 mmol) in dichloromethane (30 mL) in an ice bath was added EDCI (0.077 g, 0.40 mmol). The solution was stirred in ice bath for 8 h and then at room temperature for 24 h. Dichloromethane (20 mL) was added and the solution was washed with water (30 mL) and brine (30 mL × 2), then dried over sodium sulfate. After the solvent was removed, the residue was chromatographed (CH_2C_2/EtOH 40:1). Compound **1c** was obtained as an orange solid (0.24 g, 58%). Mp 189−191 °C. $[\alpha]^{20}_D$ −26.3 (*c* 1.38, $CHCl_3$).^{1}H NMR (DMSO-d_6) *δ* 8.43 (m, 2 H), 8.05 (s, 2 H), 8.02 (m, 2 H), 7.88 (s, br, 1 H), 7.78−7.64 (m, 4 H), 7.36−7.30 (m, 4 H), 6.93−6.86 (m, 4 H), 4.70 (s, 4 H), 4.40−4.36 (m, 2 H), 4.31−4.18 (m, 3 H), 4.08 (t, *J* = 6.3 Hz, 4 H), 3.63 (s, 3 H), 3.56 (t, *J* = 7.1 Hz, 2 H), 3.10−3.04 (m, 4 H), 1.82−1.33 (m, 17 H), 1.27−1.24 (m, 30 H), 0.88−0.82 (m, 15 H). MS (ESI) *m*/*z* 1390 $[M + Na]^+$. Anal. Calcd for $C_{77}H_{103}N_7O_{15}$: C, 67.66; H, 7.61; N, 7.17. Found: C, 67.88; H, 7.69; N, 6.87.

The following peptides were prepared according to the procedure described for **1c**.

Tetrapeptide 1d. Orange solid (44%). Mp 230−232 °C. $[\alpha]^{20}_D$ −11.0 (*c* 0.94, $CHCl_3$ (0.5% CF_3COOH)).^{1}H NMR (DMSO-d_6) *δ* 8.50−8.47 (m, 3 H), 8.13 (s, 2 H), 8.12−8.00 (m, 5 H), 7.90 (s, br, 1 H), 7.76−7.60 (m, 4 H), 7.37−7.25 (m, 4 H), 6.91−6.84 (m, 4 H), 4.70 (s, 4 H), 4.38−4.20 (m, 8 H), 4.07 (t, *J* = 6.4 Hz, 4 H), 3.63 (s, 3 H), 3.58 (t, *J* = 6.7 Hz, 4 H), 3.08 (s, br, 6 H), 1.85−1.23 (m, 63 H), 0.88−0.82 (m, 18 H). MS (MALDI-tof) *m*/*z* 1871 $[M + Na]^+$. Anal. Calcd for $C_{102}H_{133}N_{11}O_{21}$: C, 66.23; H, 7.26; N, 8.33. Found: C, 65.85; H, 7.43; N, 8.14.

Pentapeptide 1e. Orange solid (34%). Mp 252−254 °C. $[\alpha]^{20}_D$ −7.90 (*c* 1.17, $CHCl_3$ (0.5% CF_3COOH)). ^{1}H NMR (DMSO-d_6) *δ* 8.49−8.45 (m, 4 H), 8.22−7.91 (m, 11 H), 7.74−7.54 (m, 4 H), 7.31−7.24 (m, 4 H), 6.89−6.82 (m, 4 H), 4.69 (s, 4 H), 4.38−4.28 (m, 11 H), 4.06 (s, br, 4 H), 3.63−3.57 (m, 9 H), 3.07 (s, br, 8 H), 1.84−1.23 (m, 79 H), 0.86−0.82 (m, 21 H). MS (MALDI-tof) *m*/*z* 2354 $[M + Na]^+$. Anal. Calcd for $C_{127}H_{163}N_{15}O_{27}\cdot H_2O$: C, 64.90; H, 7.09; N, 8.94. Found: C, 64.41; H, 7.23; N, 8.86.

Pentapeptide 1f. Orange solid (44%). Mp 222−224 °C. $[\alpha]^{20}_D$ −13.0 (*c* 1.14, $CHCl_3$ (0.5% CF_3COOH)). ^{1}H NMR (DMSO-d_6) *δ* 8.53−8.45 (m, 3 H), 8.13−7.97 (m, 10 H), 7.78−7.63 (m, 6 H), 7.34−7.25 (m, 6 H), 6.91−6.85 (m, 6 H), 4.70 (s, 6 H), 4.48−4.23 (m, 9 H), 4.04 (s, br, 6 H), 3.64−3.50 (m, 7 H), 3.05 (s, br, 8 H), 1.81−1.17 (m, 79 H), 0.88−0.81 (m, 21 H). MS (MALDI-tof) *m*/*z* 2299 $[M + Na]^+$. Anal. Calcd for $C_{127}H_{167}N_{13}O_{25}\cdot H_2O$: C, 66.49; H, 7.44; N, 7.94. Found: C, 66.45; H, 7.48; N, 8.01.

Hexapeptide 1g. Orange solid (31%). Mp 248−250 °C. $[\alpha]^{20}_D$ −8.60 (*c* 1.38, $CHCl_3$ (0.5% CF_3COOH). ^{1}H NMR (DMSO-d_6) *δ* 8.52−8.45 (m, 5 H), 8.22−7.94 (m, 12 H), 7.80−7.52 (m, 6 H), 7.33−7.20 (m, 6 H), 7.00−6.82 (m, 6 H), 4.69 (s, 6 H), 4.38−4.20 (m, 12 H), 4.05 (s, br, 6 H), 3.62−3.50 (m, 9 H), 3.06 (s, br, 10 H), 1.81−1.13 (m, 95 H), 0.85−0.82 (m, 24 H). MS (MALDI-tof) *m*/*z* 2759 $[M + H]^+$. Anal. Calcd for $C_{152}H_{197}N_{17}O_{31}\cdot 3H_2O$: C, 64.91; H, 7.29; N, 8.49. Found: C, 64.77; H, 7.26; N, 8.83.

Computational Method. The folding patterns were constructed by using the Builder program within the package HyperChem.[30] Then they were optimized by the conjugate gradient with the AMBER force field and the RMS derivative criteria of 0.00001 kcal/mol. To search for conformational space and explore lower energy conformation on the potential energy surface, molecular dynamics calculations were performed without constraints. After 100 ps of molecular dynamics simulation, an additional round of energy minimization was again completed. Molecular mechanics and molecular dynamics are used to obtain the geometry of the large molecule.[31] To compare the estimated computational data, the single-point energies were also calculated by using the B3LYP/6-31G method. The density function method B3LYP is a Beck's three-parameter hybrid method, using the Lee−Yang−Parr correlation function,[32] which includes both local and nonlocal terms, and a Vosko−Wilk−Nusair correlation function[33] referred to as local spin density correlation. The method has been shown to yield quite accurate results for the energy and geometry of organic compounds.[34]

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Supporting Information Available: NOESY spectra of compounds **1b**, **1c**, and **1d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(30) Hyperchem 5.1 for windows; Hypercube Inc.: 1115 NW 4th Street, Gainesville, FL 32601-4256.

(31) (a) Chen, G.; Cruz, R.; Martinze, M.; Lara-Ochoa, F. *J. Mol. Struct. (THEOCHEM)* **2000**, *496*, 73. (b) Cheng, Y.; Yang, Z.; Tan, H.; Liu, R.; Chen, G.; Jia, Z. *Biophys. J.* **2002**, *83*, 2202.

(32) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

(33) Vosko, S. H.; Wilk, L.; Nusair, M. *Can. J. Phys.* **1980**, *58*, 1200.

(34) (a) Chen, G.; Liu, R.; Silaghi-Dumitrescu, I.; Espinoza-Perez, G.; Zentella-Dehesa, A.; Lara-Ochoa, F. *Int. J. Quantum Chem.* **2001**, *83*, 60. (b) Chen, G.; Su, S.; Liu, R. *J. Phys. Chem. B* **2002**, *106*, 1570. (c) Tan, H.; Qu, W.; Chen, G.; Liu, R. *Chem. Phys. Lett.* **2003**, *369*, 556.