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Phenanthroline Dicarboxamide-Based Helical Foldamers: Stable Helical Structures in Methanol

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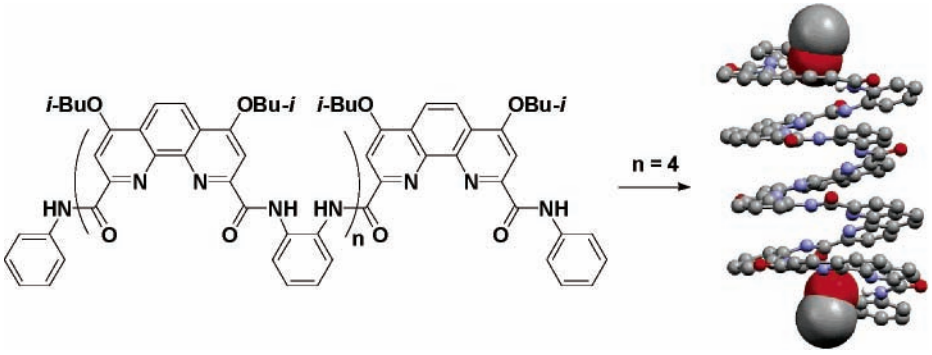

A series of new aromatic oligoamides **2**−**5** based on 1,10-phenanthroline diacid and *o*-phenylenediamine have been synthesized through a convergent segment coupling strategy. These oligomers can fold into well-defined helical structures in solution through intramolecular hydrogen bonds and aromatic stacking interactions, which has been established by ^{1}H NMR, fluorescence, and UV/vis spectra. In particular, it was found that the oligomers were more favorable to fold into stable helical structures in methanol than in chloroform and dichloromethane. The helical foldamers formed in the solid state have been characterized by single-crystal X-ray diffraction analysis. The results showed that the high curvature of the strands led to one and a half turns for both **2** and **21**, three turns for **4**, and nearly four turns for **5**.

Introduction

Inspired by the fact that helices are not only key structure features of many biological macromolecules but are also important in material science, synthetic oligomers that fold into well-defined helical secondary structures are of considerable interest in biomimetic and synthetic supramolecular chemistry.[1,2] Consequently, great efforts have been made in the development of helical oligomers during the past decade. According to the structural features, the existing helical oligomers can be classified as (1) peptidomimetic helices,[3−11] (2) nonbiologically derived helices,[12−14] and (3) helicates[15] in which helical foldamers were formed with metal coordination as the driving force.

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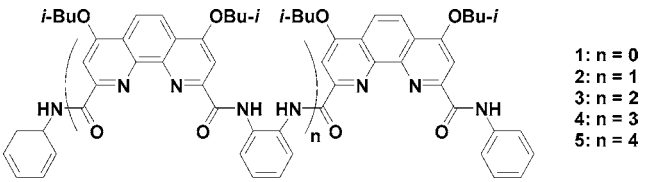
Recently, aromatic oligoamides[16] that can adopt helical conformations have received increasing attention, for they feature a remarkable combination of structural predictability, stability, tunability, and ease of synthesis. However, only a few classes of the helical aromatic oligoamides including oligoanthranilamides,[17] oligopyridine-dicarboxamides,[18] quinoline-derived oligoamides,[19] and meta-connected diaryl amides[20] have been developed up to now. In particular, because the folding of these strands into helices mainly relies on intramolecular hydrogen bonds, competitive intermolecular hydrogen bonds make the helix formation less significant in polar solvents.[18b] As a result, the folding behavior of the aromatic oligoamides is mainly investigated in an apolar solvent such as $CHCl_3$. So far, no detailed reports[18f,21] can be found for aromatic oligoamides to fold into helical structures in protonic solvent such as methanol or water, although it is important when these oligomers are considered as potential models of biological macromolecules.

CHART 1



Herein, we report the design and synthesis of a series of new aromatic oligoamides, **2**−**5** (Chart 1), which can fold into well-defined helical secondary structures in solution and in the solid state through intramolecular hydrogen bonds and aromatic stacking interactions. It is particularly noted that the aromatic oligoamides can form more stable helical structures in methanol than in chloroform and dichloromethane.

Results and Discussion

Consideration in Design. The aromatic oligoamides **2**−5 were designed and synthesized by alternating 1,10-phenanthroline-2,9-diacid and *o*-phenylenediamine. Both the diacid and the diamine units define angles of 60°, which leads to the high bending of the strands and strong $\pi-\pi$ stacking interactions between two adjacent phenanthroline units. More reasons for the phenanthroline unit selected as the building block include the following: (1) two nitrogen atoms in the phenanthroline unit are hydrogen-bond acceptors and can form intramolecular hydrogen bonds with amide hydrogens to restrict the conformations of the strands; (2) when the strands fold into helical structures, the aromatic stacking interactions between the phenanthroline units can further stabilize the formed helical structures; (3) the phenanthroline unit makes the folding behavior of the oligomers **2**−**5** in solution conveniently investigated by the UV/vis and fluorescence spectra. Moreover, two *iso*-butoxy groups are introduced into the four and seven positions of the phenanthroline unit for the solubility of the oligomers.

Synthesis of the Oligomers. A convergent segment coupling strategy was used for the synthesis of the aromatic oligoamides **2**−**5**. A synthesis of **2** is outlined in Scheme 1. With **6** as the starting material,[19c] **7** was prepared by the saponification with KOH and then a condensation with aniline via carbonyl chloride. Through a catalytic hydrogenation of **7**, an addition to dimethyl acetylenedicarboxylate, and then a thermal closure reaction, compound **10** was obtained. An alkylation of **10** under Mitsunobu conditions afforded **11**, which was then saponified under similar conditions to give the acid **12**. The coupling of **12** and 1.5 equiv of aniline in the presence of DCC gave **1** in 75% yield. Similarly, **2** was obtained in 51% yield by the coupling of **12** and 0.5 equiv of *o*-phenylenediamine. When excess

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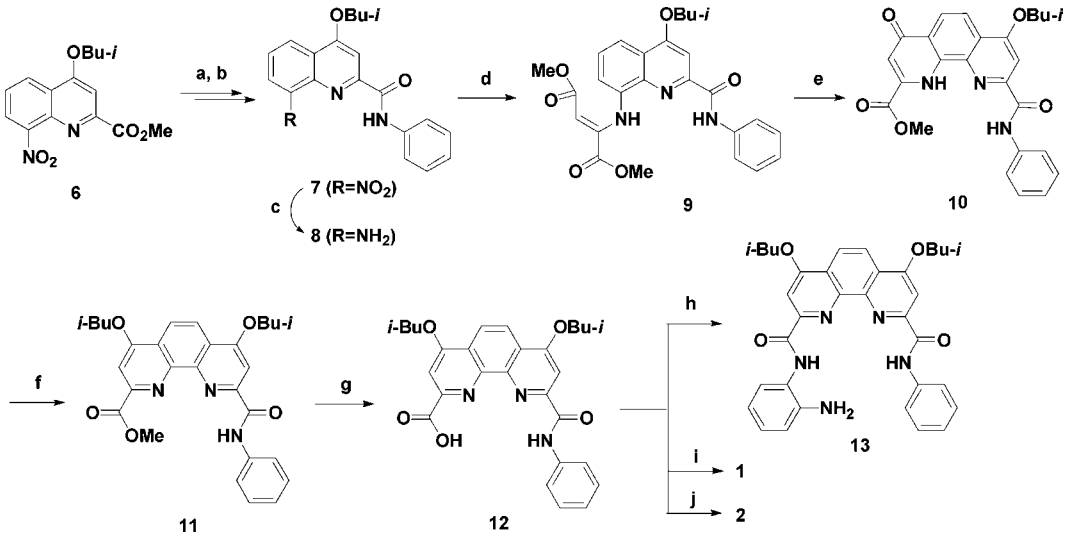
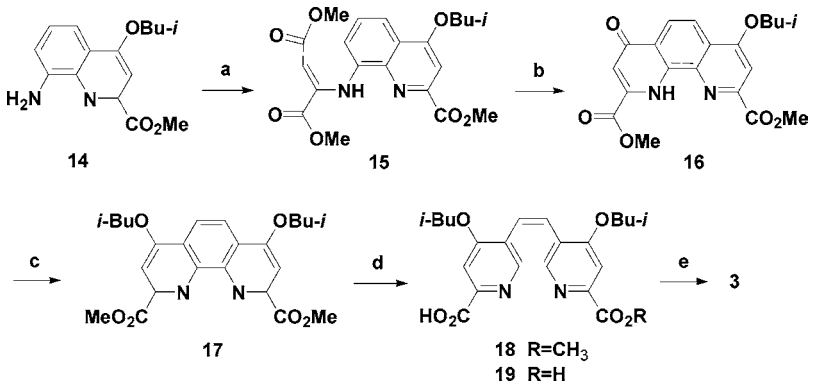
SCHEME 1 [a]



[a] Reagents and conditions: (a) KOH, THF/MeOH; (b) $SOCl_2$, reflux, aniline, CH_2Cl_2, Et_3N, rt, 93%; (c) H_2, Pd/C, CH_2Cl_2, rt, 100%; (d) dimethyl acetylenedicarboxylate, MeOH, rt, 71%; (e) diphenyl ether, reflux, 54%; (f) *iso*-butanol, Ph_3P, DEAD, rt, 72%; (g) KOH, THF/MeOH, 100%; (h) DCC, CH_2Cl_2, excess *o*-phenylenediamine, 71%; (i) DCC, CH_2Cl_2, 1.5 equiv aniline, 75%; (j) DCC, CH_2Cl_2, 0.5 equiv *o*-phenylenediamine, 51%.

SCHEME 2 [a]



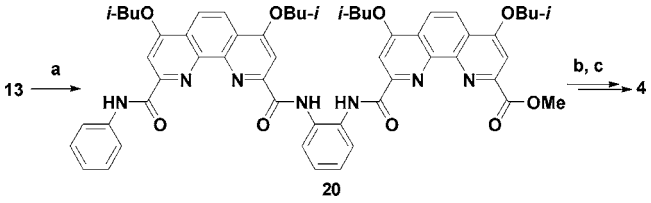
[a] Reagents and conditions: (a) dimethyl acetylenedicarboxylate, MeOH, rt, 75%; (b) diphenyl ether, reflux, 74%; (c) 2-bromobutane, K_2CO_3, DMF, 80 °C, 82%; (d) KOH, THF/MeOH, 85% for **18** and 100% for **19**; (e) **19** and **13**, DCC, CH_2Cl_2, 51%.

o-phenylenediamine (>6 equiv) was used, the monoamine **13** was obtained in 71% yield from **12**. Compound **13** is a key intermediate for the synthesis of oligomers **3** and **4**.

As shown in Scheme 2, compound **16** was synthesized by the thermal closure of **15,** which was obtained by the addition of **14**[19c] to dimethyl acetylenedicarboxylate. It was found that **16** could not be alkylated under Mitsunobu conditions but could react with 2-bromobutane in DMF in the presence of K_2CO_3 to give compound **17** in 82% yield. Through the control of the quantity and the drop rate of KOH dissolved in methanol at 0 °C, the monoacid **18** could be obtained in 85% yield by the partial hydrolysis of **17**. If excess KOH was used, the diacid **19** was obtained in quantitative yield. The coupling of **19** and 2 equiv of **13** in the presence of DCC gave the oligomer **3** in 51% yield.

The reaction of **13** and monoacid **18** gave **20**, which was saponified, followed by a condensation with 0.5 equiv of *o*-phenylenediamine in the presence of DCC to give the oligomer **4** (Scheme 3). Similarly, compound **21** was obtained if excess *o*-phenylenediamine was used. The monoamine **21** reacted with monoacid **18** to afford the prolonged ester **22**, which was hydrolyzed and further coupled with **21** to give the desired

SCHEME 3 [a]



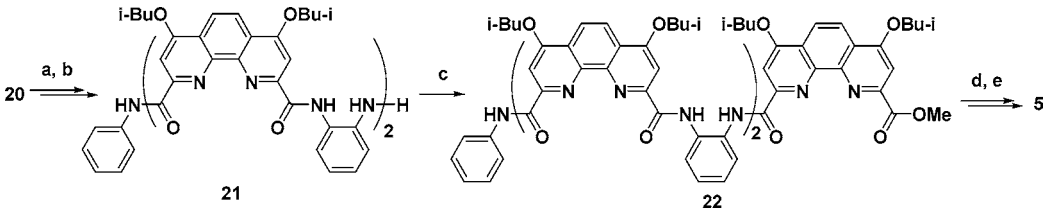
[a] Reagents and conditions: (a) DCC, CH_2Cl_2, 1.2 equiv **18**, 75%; (b) KOH, THF/MeOH, rt; (c) DCC, CH_2Cl_2, 0.5 equiv *o*-phenylenediamine, 45%.

oligomer **5** in moderate yield (Scheme 4). All of the intermediates and target compounds have good solubility in chlorinated solvents, but they are almost insoluble in DMSO.

Formation of Helical Secondary Structures in Solution. The conformations of **2**−**5** in solution were investigated through ^{1}H NMR, UV/vis, and fluorescence spectral methods.

The assignments of the ^{1}H NMR spectra of **2** and **3** in $CDCl_3$ are based on COSY experiments and a comparison with the spectrum of compound **1**. As is expected for involving intramolecular hydrogen bonds, the amide protons of **2** are deshield-

SCHEME 4 [a]



[a] Reagents and conditions: (a) KOH, THF/MeOH, rt; (b) DCC, CH_2Cl_2, excess *o*-phenylenediamine, 65%; (c) DCC, CH_2Cl_2, 1.2 equiv **18**, 63%; (d) KOH, THF/MeOH, rt; (e) DCC, CH_2Cl_2, 0.83 equiv **21**, 42%.

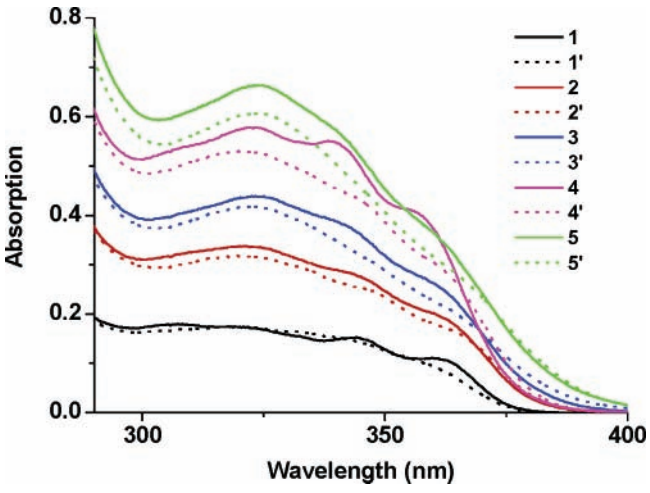


FIGURE 1. Electronic absorption spectra of **1**−**5** in dichloromethane (solid lines, 1−5) and in methanol (dot lines, 1′−5′), $c = 1 \times 10^{-5}$ M.

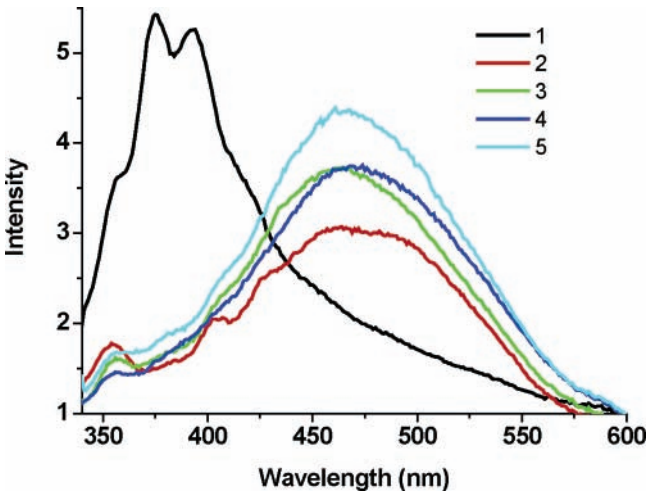


FIGURE 2. Fluorescence emission spectra of **1**−**5** in dichloromethane ($\lambda_{ex} = 320$ nm, $c = 1 \times 10^{-5}$ M).

ed at 11.21 and 10.42 ppm, and those of **3** are deshielded at 10.96, 10.55, and 10.37 ppm, respectively. The terminal benzene proton signals in **1** are located at 7.92, 7.43, and 7.21 ppm, respectively, whereas they are located at 7.65, 7.31, and 7.13 ppm in **2** and at 7.54, 7.16, and 7.03 ppm in **3**. Moreover, the phenanthroline proton signals of **2** and **3**[22] also show upfield shifts compared with that of **1**.[23] These results reveal that aromatic stacking interactions exist in the oligomers **2** and **3**. The ^{1}H NMR spectra of **4**[24] and **5** at room temperature are too complicated to be assigned, but it can still be found that most of the aromatic protons in **4** and **5** are shielded at lower than 7.00 ppm, which is also consistent with the formation of the helical structures in $CDCl_3$ involving the aromatic overlaps.

It is important to examine the intramolecular interactions through the electron absorption spectra, because the formation of helical structures will lead to stacking of phenanthroline units. Consequently, the UV/vis spectra of compounds **1**−**5** were recorded in dichloromethane and shown in Figure 1 (solid lines). The broad band between 300 and 375 nm represents the absorption of the phenanthroline unit. For **1**−**5**, the molar extinction coefficients, ϵ, at 324 nm are 18 000, 33 700, 43 800, 57 800, and 66 400 $M^{-1}cm^{-1}$, respectively. Compared with **1**, red shifts of **2**−**5** are not obvious. But a decrease in the absorption coefficients was observed when the number of phenanthroline units in **1**−**5** were considered, which implied that the helical ordering and stacking of the phenanthroline units in **2**−**5** existed.[12e] To rule out intermolecular association, the ϵ for each oligomer was determined by using a range of concentrations.[23] For each compound, Beer's law behavior was observed, which indicated that the oligomers were in an ordered conformation consistent with the helix formation.[14a]

Further evidence for the helical features of **2**−**5** came from their fluorescence spectra.[23] All of the fluorescence experiments were carried out in dichloromethane, and the excitation wavelength was selected at 320 nm. As shown in Figure 2, compound **1** showed a typical phenanthroline emission. In the cases of **2**−**5**, the phenanthroline emission decreased while a new broad red-shifted band at about 475 nm was observed. The broad band at the longer wavelength could be attributed to the excimer resulting from the self-organized stacking of the phenanthroline units in the helix.[12f,14a]

The formation of the aromatic oligoamide-based helical foldamers reported so far is driven by intramolecular hydrogen bonds, which are strong in a low polar solvent such as $CHCl_3$. However, we found that **2**−**5** could fold into more stable helical structures in CH_3OH than in $CHCl_3$. As shown in Figures 3 and 4, the ^{1}H NMR spectra of **2** and **3** in methanol-d_4 feature sharper peaks than those in $CDCl_3$.[25] Moreover, most of the aromatic proton signals of **2** and **3** in methanol-d_4 move upfield compared to those in $CDCl_3$. The proton signals of the three and eight positions of the phenanthroline unit in **2** shift from 7.69 and 7.61 ppm in $CDCl_3$ to 7.49 and 7.44 ppm in methanol-d_4. In the case of **3**, the proton signals of the three and eight

(22) They are overlapped with other aromatic proton signals and can not be unambiguously assigned.

(23) See Supporting Information.

(24) ^{1}H NMR spectra of **4** in $CDCl_3$ were measured at various concentrations,[23] which indicated that the intermolecular aggregation might play a role in the not so well-resolved peaks.

(25) In the experiments, 10−20% $CHCl_3$ was added to completely dissolve the samples.

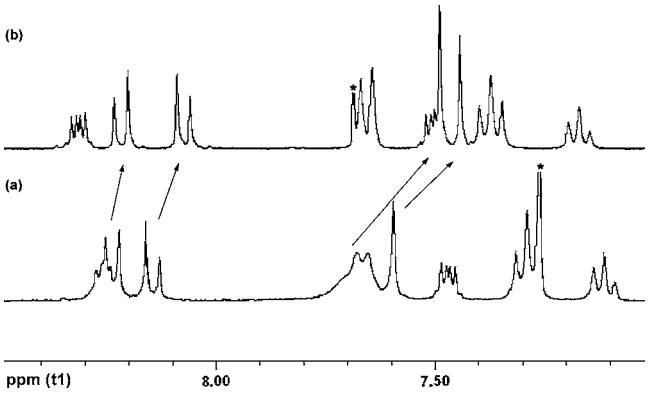


FIGURE 3. Comparison of partial ^{1}H NMR spectra for **2** in (a) $CDCl_3$ and (b) $CD_3OD/CDCl_3$ (4:1); the arrows point out the corresponding signals.

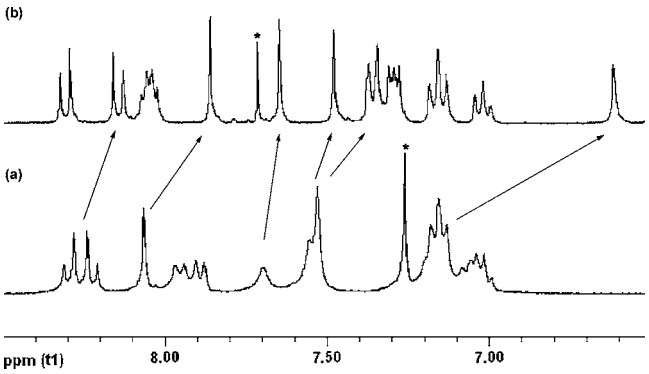


FIGURE 4. Comparison of partial ^{1}H NMR spectra for **3** in (a) $CDCl_3$ and (b) $CD_3OD/CDCl_3$ (4:1); the arrows point out the corresponding signals.

positions of the phenanthroline shift from about 7.72, 7.56, and 7.10 ppm in $CDCl_3$ to 7.62, 7.51, and 6.62 ppm in methanol-d_4, and the proton signals of the five and six positions of the middle phenanthroline unit shift from 8.07 to 7.86 ppm. It is different from **2** and **3** that no obvious spectra changes of **1** in methanol-d_4 and in $CDCl_3$ occurred.[23] These observations imply that strong aromatic stacking interactions exist in **2** and **3**, which result in the more stable helical conformations in methanol than in chloroform. A direct reason for the enhanced stability of the helical structures in methanol may be the intermolecular hydrogen bonds between the methanol molecules and the helices, as shown in the solid state, which is also proved by the comparison of the ^{1}H NMR spectra for **2** in $CDCl_3$ and $D_2O/CDCl_3$.[23]

A NOESY experiment of **3** in methanol-d_4 displayed the expected correlations for the formation of a helical structure in solution. As shown in Figure 5, four cross peaks are observed. Two of them are between ortho proton H_a and meta proton H_b of the carboxamide group in the terminal benzene ring and proton H_e of the center phenanthroline unit. The third one is between proton H_d of the side phenanthroline unit and ortho proton H_g of the carboxamide group in the *o*-phenylenediamine ring. The fourth one is between proton H_c of the side phenanthroline unit and proton H_f of the center phenanthroline unit. These contacts provide the most diagnostic evidence of a helical structure of **3** in a methanol solution.

The formation of stable helical structures of **2**−**5** in methanol is further proved by the electronic absorption spectra. A comparison of the UV spectra of **1** in CH_2Cl_2 and CH_3OH shows that the absorption intensities remain unchanged. However, the UV spectra of **2**−**5** exhibit that their absorption intensities in methanol are all lower than those in CH_2Cl_2 (Figure 1, dotted lines), which indicates that strong aromatic stacking interactions in **2**−**5** exist. As a result, the more stable helical structures were formed in methanol compared with those formed in dichloromethane.[14a,12e]

Formation of Helical Secondary Structures in the Solid State. Single crystals of **2**, **4**, **5**, and **21**, suitable for X-ray analysis, were obtained from the mixture of CH_2Cl_2/CH_3OH through a slow evaporation at room temperature. As shown in Figure 6, the oligomers **2**, **4**, **5**, and **21** all adopt regular helical secondary structures in the solid state. The high curvature of the strands leads to one and a half turns for both **2** and **21**, three turns for **4**, and nearly four turns for **5**. The four crystal structures all belong to the centrosymmetric space group, and a pair of right- and left-handed helical strands are presented in their unit cells. The helical foldamer of **5** adopts a perfect C_2 symmetrical structure, meanwhile, the helices formed by **2**, **4**, and **21** slightly deviate from a C_2 symmetry.

It is different from the helical structures of the oligopyridinedicarboxamides,[18] in which a slight deviation from the preferred planar conformation of the molecular strand owing to the formation of a helix consecutively distributes among all the pyridine rings. Crystal structures of **2**, **4**, **5**, and **21** show that the deviations are mainly imposed on the *o*-phenylenediamine rings and that the dihedral angles between the *o*-phenylenediamine ring and the two adjacent phenanthroline units are different. Moreover, it can be found that the longer the oligomers are, the smaller the average dihedral angles are. For **2** and **21**, the dihedral angles are about 30−40°, which are about 10−20° for **5**. The helical pitches in the foldamers are all about 3.4 Å, which are consistent with those of other helical aromatic oligoamides.[16b] In all cases, the two adjacent phenanthroline units partly overlap and form consecutive aromatic stacking with a centroid distance of about 3.5 Å, which is helpful to stabilize the helical structures.

In the helices, all the hydrogen atoms of the amide groups point inward, while the oxygen atoms of the carbonyl groups point outward. Moreover, the inner rims of the helices all adopt a conformation similar to that of the penta-aza-15-crown-5 macrocycle. There are six methanol molecules in the unit cell of **2**, four of which are presented at the ends of the two helices, and the other ones are located between the helices. Similarly, there also exist methanol molecules in the crystals of **5** and **21**, part of which are presented at the ends of the helices.[23] The intermolecular hydrogen bonds between the methanol molecules and the helices may play an important role in the enhanced helical stability, which is consistent with the behavior of the helical foldamers in methanol. In the crystal of **4**, no methanol molecules were found, but eight water molecules were found in the unit cell. They are all located between the helices.

Conclusion

In conclusion, we have presented a new class of aromatic oligoamide helical foldamers and demonstrated that the phenanthroline dicarboxamide-based oligomers could fold into well-defined helical structures in solution and in the solid state through intramolecular hydrogen bonds and aromatic stacking interactions. In particular, it was found that the aromatic oligoamides could form more stable helical structures in methanol compared with those formed in chloroform and

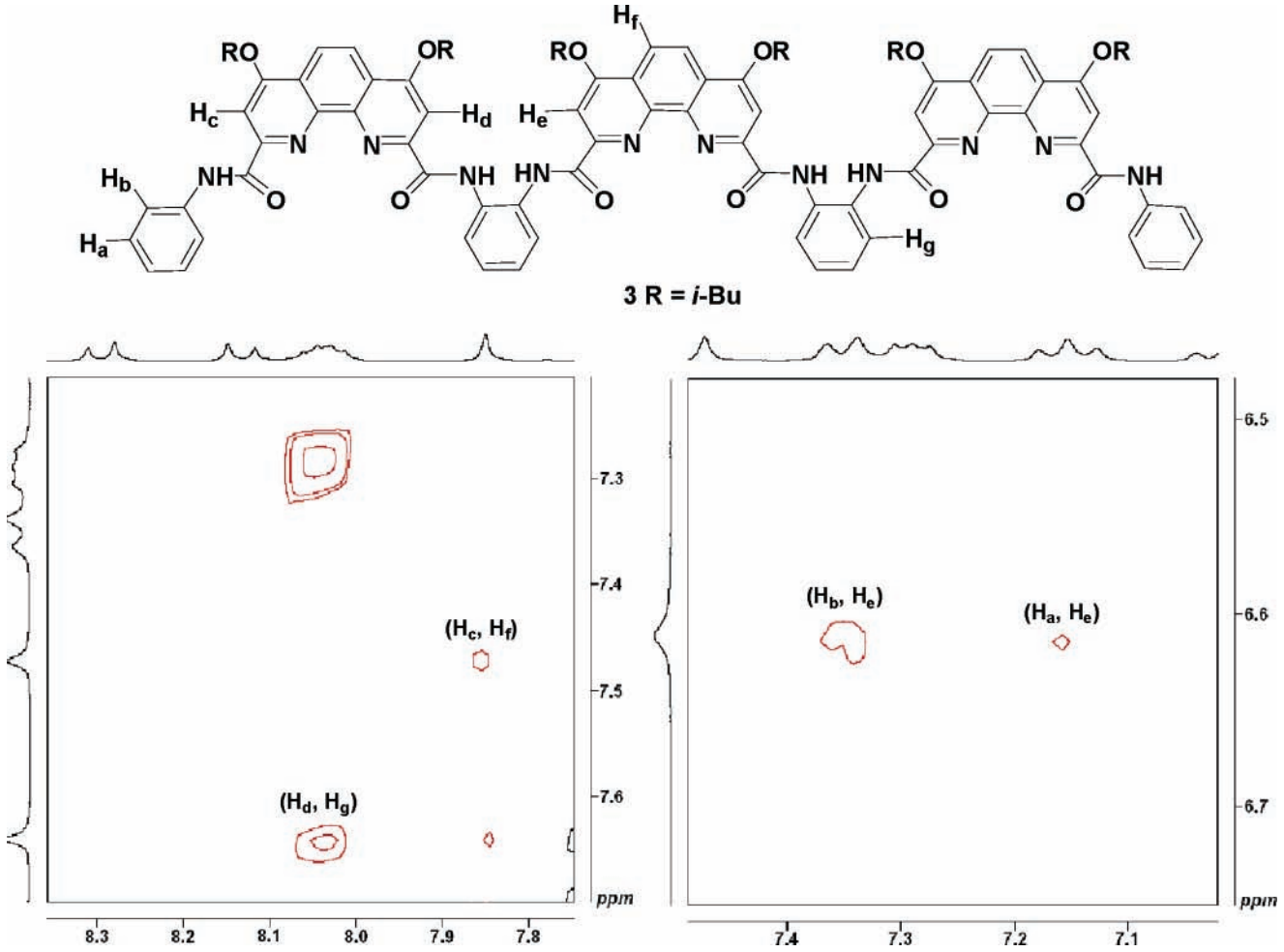


FIGURE 5. NOESY spectrum of **3** in $CD_3OD/CDCl_3$ (4:1).

dichloromethane, which may promote the aromatic oligoamide-based helical foldamers for potential applications in biology and material science.

Experimental Section

Compound 13. To the mixture of the acid **12**[23] (487 mg, 1 mmol) and excess *o*-phenylenediamine (648 mg, 6 mmol) in CH_2Cl_2 (15 mL) cooled to 0 °C was added DCC (226 mg, 1.1 mmol). After being stirred at room temperature for 24 h, the reaction mixture was filtered to remove the solid, concentrated, and then washed with hot methanol to give the pure product **13** as a yellow solid (0.41 g, 70.5%). Mp 242−244 °C. ^{1}H NMR ($CDCl_3$): δ 10.89 (s, 1H), 10.66 (s, 1H), 8.28 (s, 2H), 7.97 (s, 2H), 7.87 (m, 3H), 7.36 (t, J = 7.6 Hz, 2H), 7.15 (m, 2H), 6.97 (t, J = 8.6 Hz, 1H), 6.86 (d, J = 8.5 Hz, 1H), 4.12 (d, J = 6.5 Hz, 4H), 3.4 (br, 2H), 2.38−2.25 (m, 2H), 1.18 (m, J = 6.7 Hz, 6H), 1.18−1.15 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 163.4, 163.2, 162.2, 162.0, 150.8, 150.6, 144.52, 144.48, 139.0, 137.7, 128.9, 126.2, 125.4, 123.1, 122.6, 122.5, 120.45, 120.37, 120.1, 118.0, 101.4, 101.3, 75.5, 75.4, 28.2, 19.2. MALDI-TOF MS (*m*/*z*): 577 $[M]^+$. Anal. Calcd for $C_{34}H_{35}N_5O_4$: C, 70.69; H, 6.11; N, 12.12. Found: C, 70.35; H, 6.05; N, 12.12.

Compound 19. To the solution of the methyl ester **17**[23] (440 mg, 1 mmol) in THF (20 mL) and MeOH (11 mL) was added dropwise KOH (67 mg, 1.2 mmol) dissolved in MeOH (15 mL). The mixture solution was stirred at room temperature for 5 h, neutralized with excess AcOH, and then extracted with chloroform. The organic phase was washed with water, dried over anhydrous $MgSO_4$, and then concentrated to give the crude product, which was further purified by column chromatography to give **19** as a white solid (349 mg, 85%). Mp > 300 °C. ^{1}H NMR ($CDCl_3$): δ 9.1 (br, 1H), 8.22 (s, 2H), 7.22 (s, 1H), 7.73 (s, 1H), 4.15−4.10 (m, 4H), 4.09 (s, 3H), 2.38−2.30 (m, 2H), 1.20−1.16 (m, 12H). ^{13}C NMR ($CDCl_3$): δ 165.4, 165.3, 164.0, 162.9, 149.1, 148.9, 144.6, 143.4, 122.9, 122.6, 120.9, 120.8, 104.5, 103.5, 76.0, 75.6, 53.2, 28.2, 28.1, 19.2, 19.17. ESI-MS (*m*/*z*): 425.3 $[M - H]^+$. Anal. Calcd for $C_{23}H_{26}N_2O_6 \cdot {}^1/_4H_2O$: C, 64.10; H, 6.20; N, 6.50. Found: C, 64.11; H, 6.39; N, 6.53.

Compound 20. A mixture of the acid **19** (511 mg, 1.2 mmol), the amine **13** (577 mg, 1 mmol), and DCC (268 mg, 1.3 mmol) in CH_2Cl_2 (25 mL) was stirred at room temperature for 24 h. The workup, as described for **13**, gave the product **20** as a white solid (740 mg, 75%). Mp 268−270 °C. ^{1}H NMR ($CDCl_3$): δ 11.59 (s, 1H), 11.43 (s, 1H), 11.18 (s, 1H), 8.26 (d, J = 9.3 Hz, 1H), 8.20 (d, J = 9.3 Hz, 1H), 8.13−8.09 (m, 2H), 8.03 (d, J = 9.2 Hz, 2H), 7.94 (d, J = 8.2 Hz, 2H), 7.84 (d, J = 7.9 Hz, 2H), 7.67 (s, 1H), 7.48−7.35 (m, 3H), 7.22 (d, J = 8.0 Hz, 2H), 7.36 (t, J = 7.3 Hz, 1H), 4.16−4.13 (m, 4H), 4.00 (d, J = 6.5 Hz, 2H), 3.90 (s, 3H), 3.50 (d, J = 6.1 Hz, 2H), 2.36−2.23 (m, 3H), 2.17−2.08 (m, 1H), 1.21−1.11 (m, 18H), 1.07 (d, J = 6.7 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 165.4, 163.1, 163.0, 162.4, 151.7, 151.4, 147.9, 145.4, 144.8, 138.0, 130.4, 128.7, 126.1, 125.9, 124.1, 124.0, 122.6, 122.4, 122.3, 121.1, 120.6, 120.5, 120.0, 119.8, 103.7, 102.1, 101.72, 101.69, 75.4, 75.3, 74.7, 52.9, 28.2, 19.26. MALDI-TOF MS (*m*/*z*): 986.3 $[M + H]^+$, 1008.3 $[M + Na]^+$, 1024.4 $[M + K]^+$. Anal. Calcd for $C_{57}H_{59}N_7O_9 \cdot H_2O$: C, 68.18; H, 6.12; N, 9.76. Found: C, 68.04; H, 6.12; N, 9.56.

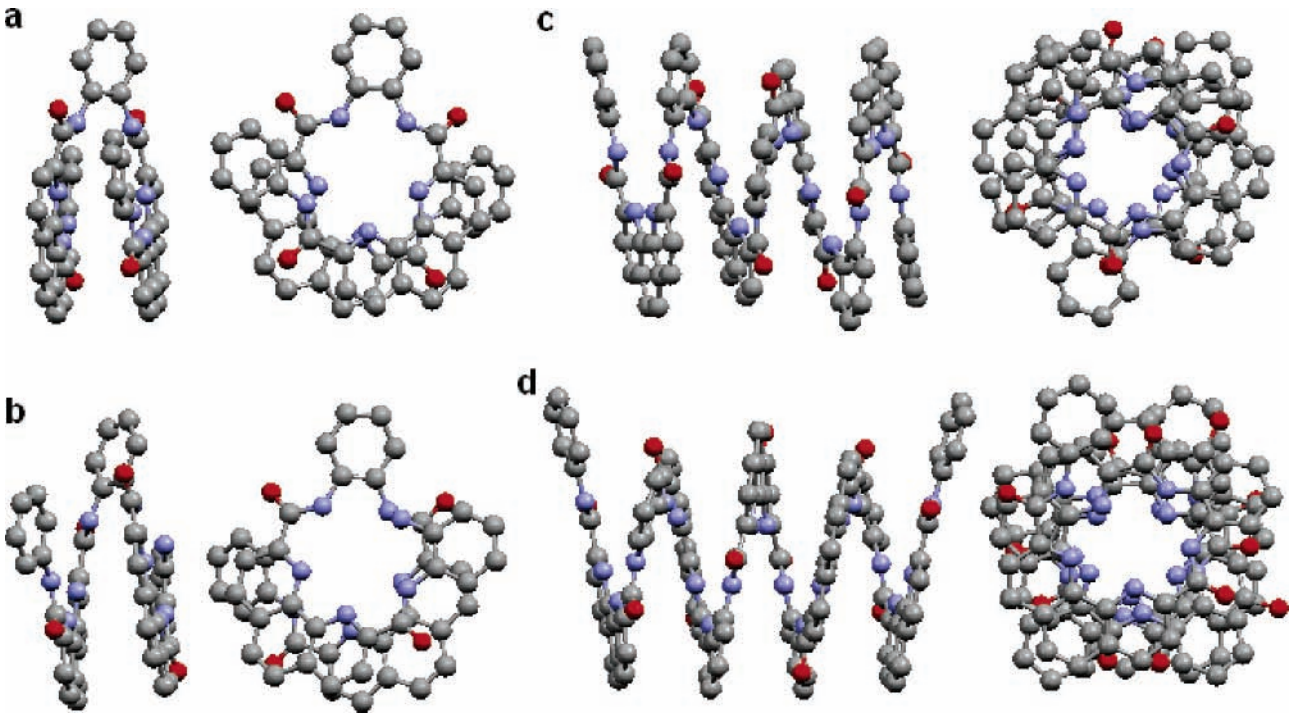


FIGURE 6. Side view (left) and top view (right) of the crystal structures of (a) **2**, (b) **21**, (c) **4**, and (d) **5**. Included solvent molecules, hydrogens, and isobutyl chains have been omitted for clarity.

Compound 21. To the solution of the methyl ester **20** (986 mg, 1 mmol) in THF (25 mL) and MeOH (15 mL) was added KOH (168 mg, 3 mmol). After being stirred at ambient temperature for 5 h, the reaction mixture was neutralized with excess AcOH and then extracted with chloroform. The organic phase was washed with water, dried over anhydrous $MgSO_4$, and then concentrated to give the acid as a white solid in quantitative yield, which was used without further purification. A mixture of the acid (972 mg, 1 mmol), excess *o*-phenylenediamine (6 mmol), and DCC (227 mg, 1.1 mmol) in CH_2Cl_2 (15 mL) was stirred at room temperature for 24 h. The workup, as described for **13**, gave the product **21** as a yellow solid (690 mg, 65%). Mp 235 °C dec. ^{1}H NMR ($CDCl_3$): δ 11.14 (s, 1H), 10.81 (s, 1H), 10.33 (s, 1H), 10.29 (s, 1H), 8.26 (d, J = 7.6 Hz, 1H), 8.19 (d, J = 9.3 Hz, 1H), 8.11−7.97 (m, 5H), 7.58 (d, J = 7.1 Hz, 2H), 7.57−7.39 (m, 6H), 7.22 (d, J = 7.6 Hz, 2H), 7.06 (t, J = 7.1 Hz, 1H), 6.97 (t, J = 6.8 Hz, 7.2 Hz, 1H), 6.86 (t, J = 7.2 Hz, 7.4 Hz, 1H), 6.65 (d, J = 7.4 Hz, 1H), 4.00 (d, J = 5.7 Hz, 2H), 3.91 (d, J = 6.2 Hz, 2H), 3.85 (d, J = 6.0 Hz, 2H), 3.57 (d, J = 5.3 Hz, 2H), 3.30 (br, 2H), 2.27−2.18 (m, 4H), 1.16−1.11 (m, 24H), 1.07 (d, J = 6.7 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 162.8, 162.4, 162.3, 161.3, 160.7, 150.8, 150.4, 149.6, 144.6, 144.3, 143.7, 137.6, 136.2, 130.5, 129.0, 128.9, 127.5, 126.1, 125.2, 124.7, 124.6, 124.4, 124.0, 122.4, 121.7, 121.6, 120.8, 120.6, 120.4, 119.9, 119.8, 119.5, 119.4, 101.7, 101.5, 100.8, 100.4, 75.3, 75.2, 74.9, 74.8, 28.24, 28.21, 28.16, 19.27, 19.27, 19.21. MALDI-TOF MS (*m*/*z*): 1062.4 $[M + H]^+$, 1084.3 $[M + Na]^+$, 1100.3 $[M + K]^+$. Anal. Calcd for $C_{62}H_{63}N_9O_8 \cdot {}^1/_2H_2O$: C, 69.52; H, 6.02; N, 11.77. Found: C, 69.64; H, 6.02; N, 11.82.

Compound 22. A mixture of the acid **19** (512 mg, 1.2 mmol), the amine **21** (1061 mg, 1 mmol), and DCC (268 mg, 1.3 mmol) in CH_2Cl_2 (25 mL) was stirred at room temperature for 48 h. The workup, as described for **13**, gave the product **22** as a yellow solid (925 mg, 63%). Mp > 300 °C. ^{1}H NMR ($CDCl_3$): δ 11.39 (s, 1H), 11.18 (s, 1H), 11.07 (s, 1H), 10.99 (s, 1H), 10.74 (s, 1H), 8.34 (d, J = 9.2 Hz, 1H), 8.24 (d, J = 9.2 Hz, 1H), 8.15−8.00 (m, 4H), 7.98 (d, J = 8.0 Hz, 1H), 7.93−7.86 (m, 2H), 7.80 (s, 1H), 7.75−7.56 (m, 6H), 7.45 (s, 1H), 7.41 (s, 1H), 7.35−7.20 (br, 3H), 7.20−7.05 (m, 3H), 7.00 (t, J = 7.3 Hz, 1H), 4.11−3.98 (br, 8H), 3.76 (s, 3H), 3.54 (d, J = 5.4 Hz, 2H), 3.21 (s, 2H), 2.39−2.16 (m, 5H), 1.55 (br, 1H), 1.25−1.12 (br, 30H), 0.63 (br, 6H). ^{13}C NMR ($CDCl_3$): δ 165.5, 163.0, 162.85, 162.80, 162.4, 162.3, 162.2, 161.9, 151.3, 150.9, 150.6, 150.5, 150.4, 147.8, 145.5, 144.9, 144.8, 144.6, 137.8, 130.9, 129.9, 129.3, 128.7, 125.6, 125.4, 125.3, 124.8, 124.0, 123.8, 123.5, 122.8, 122.5, 122.3, 122.2, 122.04, 122.00, 121.1, 120.8, 120.3, 120.1, 120.0, 119.7, 101.9, 101.6, 101.0, 75.5, 75.3, 74.4, 52.8, 28.2, 27.8, 19.3, 19.2, 18.8. MALDI-TOF MS (*m*/*z*): 1470.4 $[M + H]^+$, 1492.5 $[M + Na]^+$, 1508.4 $[M + K]^+$. Anal. Calcd for $C_{85}H_{87}N_{11}O_{13}$: C, 69.42; H, 5.96; N, 10.48. Found: C, 69.07; H, 6.02; N, 10.48.

Compound 1. A mixture of the acid **12** (487 mg, 1 mmol), aniline (140 mg, 1.5 mmol), and DCC (227 mg, 1.1 mmol) in CH_2Cl_2 (15 mL) was stirred at room temperature for 24 h. The workup, as described for **13**, gave the product **1** as a white solid (0.42 g, 75%). Mp > 300 °C. ^{1}H NMR ($CDCl_3$): δ 10.84 (s, 2H), 8.33 (s, 2H), 8.05 (s, 2H), 7.46 (d, J = 7.8 Hz, 4H), 7.45 (t, J = 7.6 Hz, 4H), 7.12 (t, J = 7.4 Hz, 2H), 4.18 (d, J = 6.5 Hz, 4H), 2.41−2.28 (m, 2H), 1.19 (d, J = 6.7 Hz, 12H). ^{13}C NMR ($CDCl_3$): δ 163.3, 162.0, 150.7, 137.8, 129.2, 124.4, 122.7, 120.5, 119.6, 101.4, 75.5, 28.2, 19.2. MALDI-TOF MS (*m*/*z*): 563.7 $[M + H]^+$, 585.7 $[M + Na]^+$. Anal. Calcd for $C_{34}H_{34}N_4O_4 \cdot {}^1/_4H_2O$: C, 72.00; H, 6.13; N, 9.88. Found: C, 72.22; H, 6.17; N, 9.92.

Compound 2. A mixture of the acid **12** (487 mg, 1 mmol), *o*-phenylenediamine (54 mg, 0.5 mmol), and DCC (227 mg, 1.1 mmol) in CH_2Cl_2 (15 mL) was stirred at room temperature for 24 h. The workup, as described for **13**, gave the product **2** as a white solid (0.27 g, 51.2%). Mp 292−294 °C. ^{1}H NMR ($CDCl_3$): δ 11.21 (s, 2H), 10.42 (s, 2H), 8.26−8.12 (m, 6H), 7.74−7.62 (m, 6H), 7.59 (s, 2H), 7.29−7.24 (m, 4H), 7.10 (t, J = 7.3 Hz, 2H), 4.12 (d, J = 6.5 Hz, 4H), 3.72 (d, J = 6.3 Hz, 4H), 2.35−2.17 (m, 4H), 1.16−1.12 (m, 24H). ^{13}C NMR ($CDCl_3$): δ 163.1 162.9, 161.4, 150.8, 145.0, 144.6, 144.4, 137.7, 129.8, 129.0, 125.9, 124.1, 122.7, 122.1, 120.7, 120.1, 119.4, 101.8, 101.1, 75.5, 75.0, 28.3, 28.2, 19.2. MALDI-TOF MS (*m*/*z*): 1047 $[M]^+$. Anal. Calcd for $C_{62}H_{62}N_8O_8$: C, 71.11; H, 5.97; N, 10.70. Found: C, 70.86; H, 5.97; N, 10.63.

Compound 3. A mixture of the acid **19** (206 mg, 0.5 mmol), the amine **13** (577 mg, 1 mmol), and DCC (227 mg, 1.1 mmol) in CH_2Cl_2 (25 mL) was stirred at room temperature for 24 h. The

workup, as described for **13**, gave the product **3** as a white solid (780 mg, 51%). Mp > 300 °C. ^{1}H NMR ($CDCl_3$): δ 10.96 (s, 2H), 10.55 (s, 2H), 10.37 (s, 2H), 8.30 (d, J = 9.2 Hz, 2H), 8.23 (d, J = 9.2 Hz, 2H), 8.07 (s, 2H), 7.94−7.86 (m, 4H), 7.72 (s, 2H), 7.55−7.51 (br, 4H), 7.17−7.12 (br, 8H), 7.05−6.98 (br, 4H), 4.09 (br, 4H), 3.68 (br, 8H), 2.40−2.16 (m, 6H), 1.20−1.14 (m, 24H), 1.06 (d, J = 6.3 Hz, 12H). ^{13}C NMR ($CDCl_3$): δ 162.8, 162.3, 162.1, 161.7, 161.1, 160.8, 150.2, 149.8, 144.1, 137.2, 130.5, 128.1, 127.0, 125.1, 124.4, 123.7, 123.1, 122.5, 121.8, 121.6, 120.5, 120.3, 120.0, 119.0, 101.6, 100.8, 100.6, 74.9, 74.5, 74.4, 27.8, 27.71, 27.68, 18.8, 18.7. MALDI-TOF MS (m/z): 1530.9 $[M]^+$, 1552.9 $[M + Na]^+$, 1569.8 $[M + K]^+$. Anal. Calcd for $C_{90}H_{90}N_{12}O_{12}\cdot 1.5H_2O$: C, 69.35; H, 5.95; N, 10.78. Found: C, 69.42; H, 6.04; N, 10.66.

Compound 4. A mixture of the acid derived from ester **20** (971 mg, 1 mmol), *o*-phenylenediamine (54 mg, 0.5 mmol), and DCC (227 mg, 1.1 mmol) in CH_2Cl_2 (15 mL) was stirred at room temperature for 24 h. The workup, as described for **13**, gave the product **4** as a yellowish solid (907 mg, 45%). Mp > 300 °C. ^{1}H NMR ($CDCl_3$): δ 10.90 (s, 2H), 10.75−10.00 (br, 6H), 8.25 (d, J = 9.2 Hz, 2H), 8.18 (d, J = 9.2 Hz, 2H), 8.09 (d, J = 9.2 Hz, 2H), 8.04 (d, J = 9.2 Hz, 2H), 7.89−7.82 (br, 4H), 7.69 (br, 4H), 7.75 (s, 2H), 7.40 (br, 4H), 7.20−6.80 (br, 16H), 4.15−4.00 (br, 4H), 3.90−3.70 (br, 4H), 3.70−3.35 (br, 8H), 2.36−2.13 (m, 8H), 1.18−1.10 (m, 48H). ^{13}C NMR ($CDCl_3$): δ 162.9, 162.7, 162.2, 162.1, 161.7, 161.6, 150.8, 150.3, 150.1, 150.0, 144.7, 144.5, 137.6, 130.1, 128.6, 125.0, 124.8, 124.7, 123.7, 122.8, 122.3, 122.2, 120.8, 120.4, 120.2, 120.1, 119.6, 101.9, 101.2, 101.1, 75.4, 75.03, 74.97, 74.8, 28.3, 28.21, 28.19, 19.3, 19.2. MALDI-TOF MS (m/z): 2016.1 $[M]^+$, 2038.1 $[M + Na]^+$. Anal. Calcd for $C_{118}H_{118}N_{16}O_{16}$: C, 70.29; H, 5.90; N, 11.11. Found: C, 69.98; H, 5.97; N, 10.97.

Compound 5. A mixture of the acid derived from the ester **22** (882 mg, 0.6 mmol), the amine **21** (530 mg, 0.5 mmol), and DCC (134 mg, 0.65 mmol) in CH_2Cl_2 (25 mL) was stirred at room temperature for 48 h. The workup, as described for **13**, gave the product **5** as a yellow solid (925 mg, 42%). Mp > 300 °C. ^{1}H NMR ($CDCl_3$): δ 11.50−9.50 (br, 10H), 8.35−7.90 (br, 11H), 7.90−7.30 (br, 17H), 7.20−6.50 (br, 18H), 4.30−3.10 (br, 20H), 2.50−2.00 (br, 10H), 1.24−0.75 (br, 60H). ^{13}C NMR ($CDCl_3$): δ 162.7, 162.6, 162.2, 162.1, 161.7, 150.8, 150.3, 150.22, 150.18, 150.13, 150.09, 150.0, 149.8, 144.71, 144.65, 144.6, 144.5, 137.6, 130.2, 130.17, 130.13, 130.07, 128.5, 125.1, 124.99, 124.95, 124.83, 124.79, 124.75, 124.70, 124.6, 124.0, 123.9, 123.6, 122.8, 122.4, 122.3, 122.1, 120.8, 120.44, 120.39, 120.1, 119.61, 119.57, 102.0, 101.9, 101.3, 101.2, 75.4, 75.02, 74.98, 74.8, 74.6, 28.2, 19.3. MALDI-TOF MS (m/z): 2500.8 $[M + H]^+$, 2522.7 $[M + Na]^+$, 2538.7 $[M + K]^+$. Anal. Calcd for $C_{146}H_{146}N_{20}O_{20}$: C, 69.42; H, 5.96; N, 11.20. Found: C, 69.72; H, 5.96; N, 11.30.

Acknowledgment. We thank the Chinese Academy of Sciences and the National Natural Science Foundation of China for financial support. We also thank the editor and the reviewers for valuable comments and suggestions.

Supporting Information Available: Synthesis of compounds **12** and **17**. Comparison of partial ^{1}H NMR spectra for **1**, **2**, and **3** in $CDCl_3$, for **1** in $CDCl_3$ and CD_3OD, and for **2** in $CDCl_3$ and $D_2O/CDCl_3$. ^{1}H NMR spectra of **4** in $CDCl_3$ at various concentrations. X-ray crystallographic data (CIF) for **2**, **21**, **4**, and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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