Conformationally constrained aromatic oligoamide foldamers with supersecondary structure motifs†

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The design, synthesis, and structural studies of aromatic foldamers based on oligo(phenanthroline dicarboxamide)s that displayed supersecondary structure motifs have been described. Governed by a combined conformational restriction, the foldamers adopted well defined and compact 3D structures, which have been validated by UV/Vis, NMR spectra, and X-ray crystal analysis. The results presented here would offer a useful route for the *de novo* design of aromatic oligoamide foldamers with distinctive structural architectures.

Introduction

The mystery of how a protein sequence specifies a unique structure and function has intrigued chemists' significant interest in the design and development of foldamers,[1] which are a kind of synthetic oligomers with definite conformational backbone structures. Consequently, considerable effort has so far focused on the creation of unnatural oligomers which are able to mimic many secondary structural elements of native peptides and proteins, such as helices,[2] sheets,[3] and turns.[4]

A supersecondary structure is the term used to describe certain common combinations of secondary structure elements that are observed frequently in protein structures.[5] In the hierarchy of protein structure classification, supersecondary structure falls between that of secondary structure and tertiary structure, which can provide a useful way of categorizing distinctive and recurring components of protein structure.[6] However, the design of highly organized protein-like supersecondary motifs from the assembly of several secondary elements is still an important challenge[7] and the X-ray crystal structures of the supersecondary conformation remain even rarer. Therefore, the developments of useful strategies to control the relative orientation of secondary building blocks within a tertiary fold play an important role in biological mimicking. In this paper, we report the design, synthesis, and structural studies in solution and in the solid state of two new series of aromatic foldamers based on oligo(phenanthroline dicarboxamide)s that display helical supersecondary structure motifs.

Recently, we have been studying a new class of aromatic oligoamides[8] based on phenanthroline dicarboxamides, which exhibited well-defined helical secondary structures in solution and in the solid state.[9] In particular, we reported[9b] the first artificial aromatic oligoamide based helix–turn–helix (HTH) supersecondary structure, which was composed of two regular helical secondary structures based on oligo(phenanthroline dicarboxamide) strands connected with a binaphthyldiamine as the turn. Subsequently, we deduced that by the insertion of suitable connecting units, we could obtain new foldamers with specific supersecondary structures easily. In addition, the rigid aromatic linkers will improve predictability and stability of the foldamers. Based on our preceding research, connected with 1,8-diaminoanthraquinone, the oligo(phenanthroline dicarboxamide)s exhibited well-defined helical secondary structures under the intramolecular hydrogen bonds (Fig. 1a). Consequently, we envisioned that changing

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† Electronic supplementary information (ESI) available: Copies of ^{1}H and ^{13}C NMR spectra. TOCSY, NOESY and UV-Vis spectra of **1**–**6**. The X-ray crystallographic files for **2** and **4**. CCDC reference numbers 720731 and 720732. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b903178b

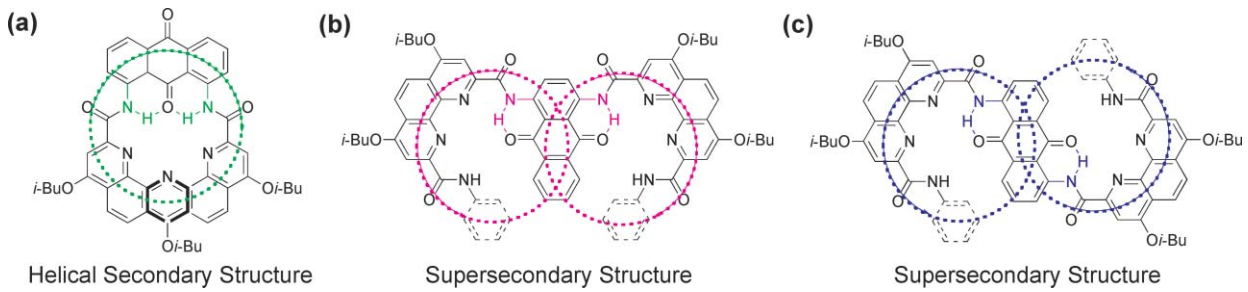


Fig. 1 Schematic representation of the projection of the two helical oligo(phenanthroline dicarboxamide) strands segments in the plane of the 1,8-diaminoanthraquinone spacer (a), 1,4-diaminoanthraquinone spacer (b) and 1,5-diaminoanthraquinone spacer (c). Overlap between the circles indicates possible steric hindrance between helices if they extend on the same side of the plane of the linkers. The arrows indicate the direction along which each oligomeric segment extends from the linker.

the amino position of the diaminoanthraquinone will cause the conformation of these oligo(phenanthroline dicarboxamide)s to change from helical structures to supersecondary structures, which would offer a useful and easy route for the *de novo* design of aromatic oligoamide foldamers with distinctive structural architectures. To confirm this thought, the new oligo(phenanthroline dicarboxamide)s **1–6** were designed and synthesized, in which the diaminoanthraquinone subunits not only are used as the linkers, but also locally set the relative orientation of the secondary elements. Because rotations about the amide nitrogen-aryl linkages at the 1 and 4 positions of the anthraquinone would be restricted by NH $\cdots$ O=C hydrogen bonds, steric hindrance was expected to prevent the two helical segments from extending on the opposite side of the linker, and the helices should be both right-handed (P-P) or both left-handed (M-M) (Fig. 1b). A similar case could also be applied in the helical supersecondary structures with 1,5-diaminoanthraquinone as the linker, in which steric hindrance would result in the two helical segments in opposite handedness (P-M) (Fig. 1c).

Results and discussion

Synthesis

As shown in Scheme 1, the oligomers **1–6** were synthesized in high yields by the reaction of the appropriate monoacid[8a] with 1,4-diaminoanthraquinone or 1,5-diaminoanthraquinone in CH_2Cl_2 in the presence of dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBt). All products have been purified by column chromatography or crystallization, and characterized by ^{1}H NMR, ^{13}C NMR, MALDI-TOF MS spectra, and elementary analyses.

UV-Vis analysis

We first examined the intramolecular interactions of the oligomers through the absorption spectra for the formation of helical structures which will lead to stacking of phenanthroline units. Consequently, the UV-Vis spectra of the oligomers **1–6** were recorded in $CHCl_3$. As shown in Fig. 2, the broad band between 300 and 400 nm represents the absorption of the phenanthroline unit. It was also found that oligomers **1–3** display absorption maxima at 343 nm and the values of their corresponding molar absorptivity were 6.0×10^4, 6.6×10^4, and 9.2×10^4 M^{-1} cm^{-1}, respectively. Similarly, the values of the molar absorptivity at 310 nm for oligomers **4–6** were found to be 4.9×10^4, 8.3×10^4, and 9.3×10^4 M^{-1} cm^{-1}, respectively. As expected, a hypochromic effect with an increased number of phenanthroline rings was shown, which implied that helical ordering and π–π* stacking of the phenanthroline units in oligomers **2**, **3**, **5**, and **6** might exist.

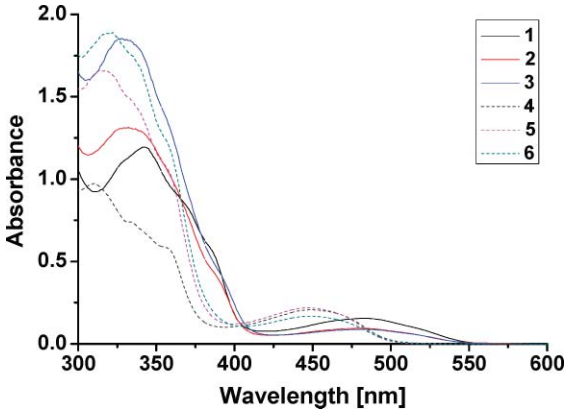
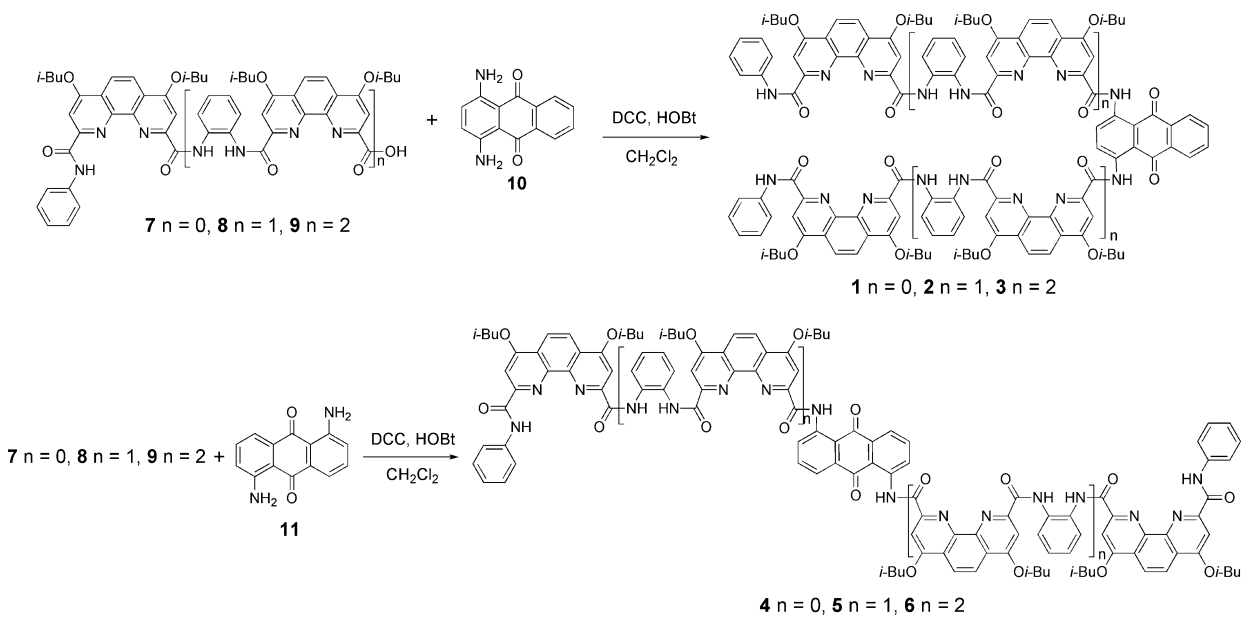


Fig. 2 UV-Vis spectra of the molecular strands **1–6** in $CHCl_3$ ($c = 2 \times 10^{-5}$ M).

NMR analysis

For further investigation of the solution-state conformation, we performed detailed NMR studies of the oligomers in $CDCl_3$ solution. With the additional TOCSY NMR data, the peaks of



Scheme 1 Synthetic schemes of compounds **1–6**.

the aromatic protons and amide protons in **1** and **2** were assigned (see ESI†). Two-dimensional NOESY ^{1}H NMR spectroscopy in $CDCl_3$ revealed the presence of close contacts between proton H_j in the anthraquinone ring and H_b in the benzene ring of **1**, which indicated that the rigid linker, 1,4-diaminoanthraquinone, locally set the relative orientation of the phenanthroline units (Fig. 3b). Additionally, the NOESY spectrum of oligomer **2** also revealed cross-peaks supporting a helical conformational preference in $CDCl_3$. For example, amide proton H_n, located on the interior ring, exhibited cross-peaks with the amide proton (H_l) and protons (H_i, H_j) on the anthraquinone ring located in regions above its position in the helix of **2** (Fig. 3c, d).

X-Ray crystal analysis

The concept was directly validated in the solid state by the single-crystal structures of oligomers **2** and **4**. The single crystal of oligomer **2** was obtained from a mixture of CH_2Cl_2, CH_3OH and CH_3CH_2OH after slow solvent evaporation at room temperature. As shown in Fig. 4a, the oligomer **2** consists of two regular helices linked by the rigid 1,4-diaminoanthraquinone, which formed a supersecondary structure. Rotations around the aryl–NH bonds of the linker are expectedly restricted by a strong intramolecular hydrogen bond between the anthraquinone oxygens and the neighboring amide protons with the C=O $\cdots$ N distance of 2.62 Å; the entire structure was held by the network of conformational restrictions. The two helical segments are found on opposite sides of the anthraquinone. If the two helices were located on the same side, they would bump into each other. Fig. 4b shows the two helices having the same handedness with a complete turn (M-M); however, the crystal is racemic with both P-P and M-M handed forms present in the unit cell (Fig. 4c), and there is an intermolecular face-to-face π–π stacking between the two phenanthroline rings of the adjacent foldamers with a distance of 3.41 Å. In the case of oligomer **4**, its crystal structure also shows (Fig. 4d, e) a clear supersecondary structure stabilized by a network of intramolecular hydrogen bonds. As expected, the rigid linker 1,5-diaminoanthraquinone sets the relative orientation of the two helical structures, and the two helical segments of oligomer **4** were also found on opposite sides of the linker. Compared with oligomer **2**, the structure of oligomer **4** possessed a center of symmetry in the middle of the anthraquinone ring. Thus, the two helices have opposite handedness, giving rise to *meso*-helicity.[10] Only one conformation (M-P) was presented in the unit cell (Fig. 4f), and there is also an intermolecular face-to-face π–π stacking between the two phenanthroline rings of the adjacent foldamers with a distance of 3.34 Å.

Conclusions

In summary, we have presented two series of artificial aromatic oligoamide based supersecondary structures, which were

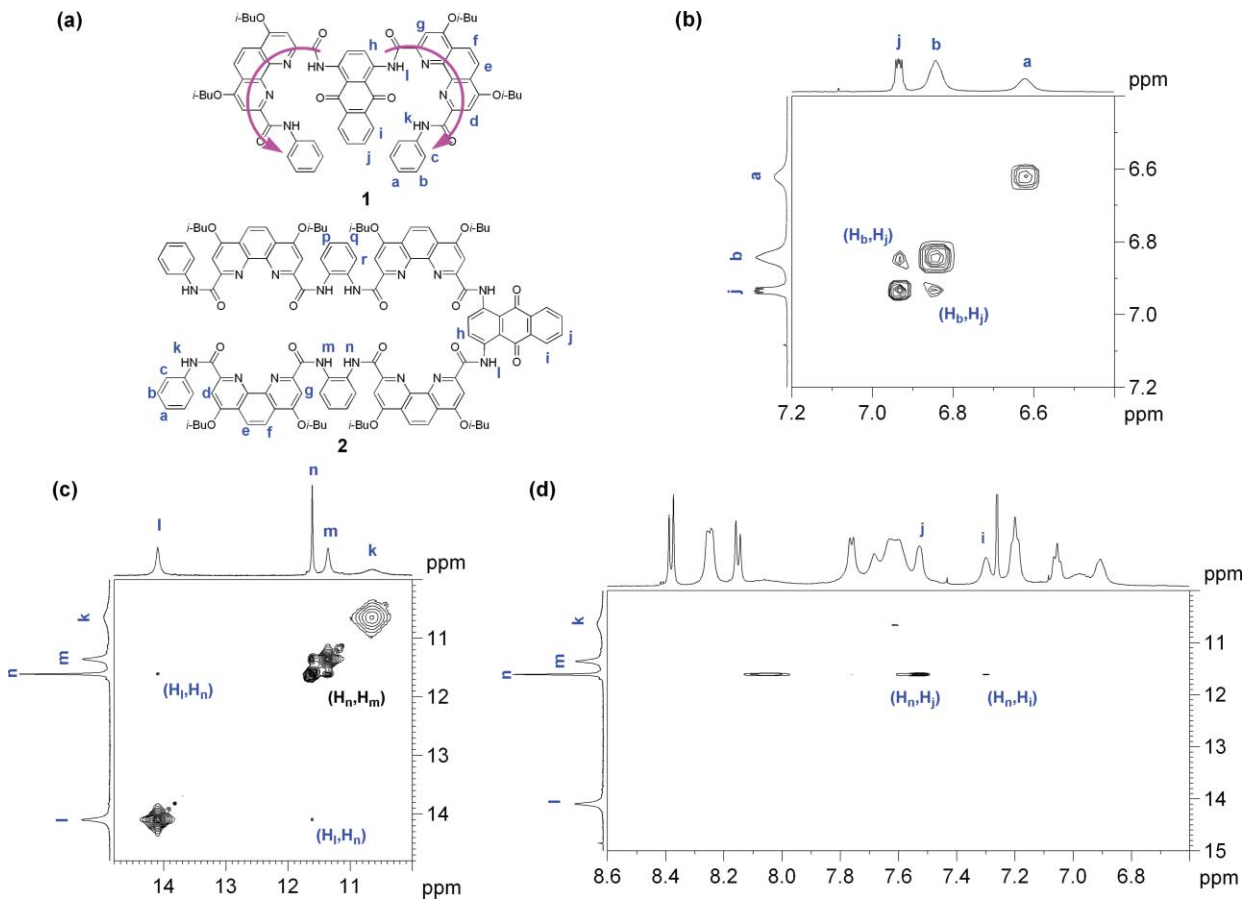


Fig. 3 (a) Molecular structures of **1** and **2** with selectively numbered protons. Partial 2D NOESY spectra (5 mM, 600 MHz, $CDCl_3$, 298 K) of (b) **1**, and (c), (d) **2** showing characteristic nOe.

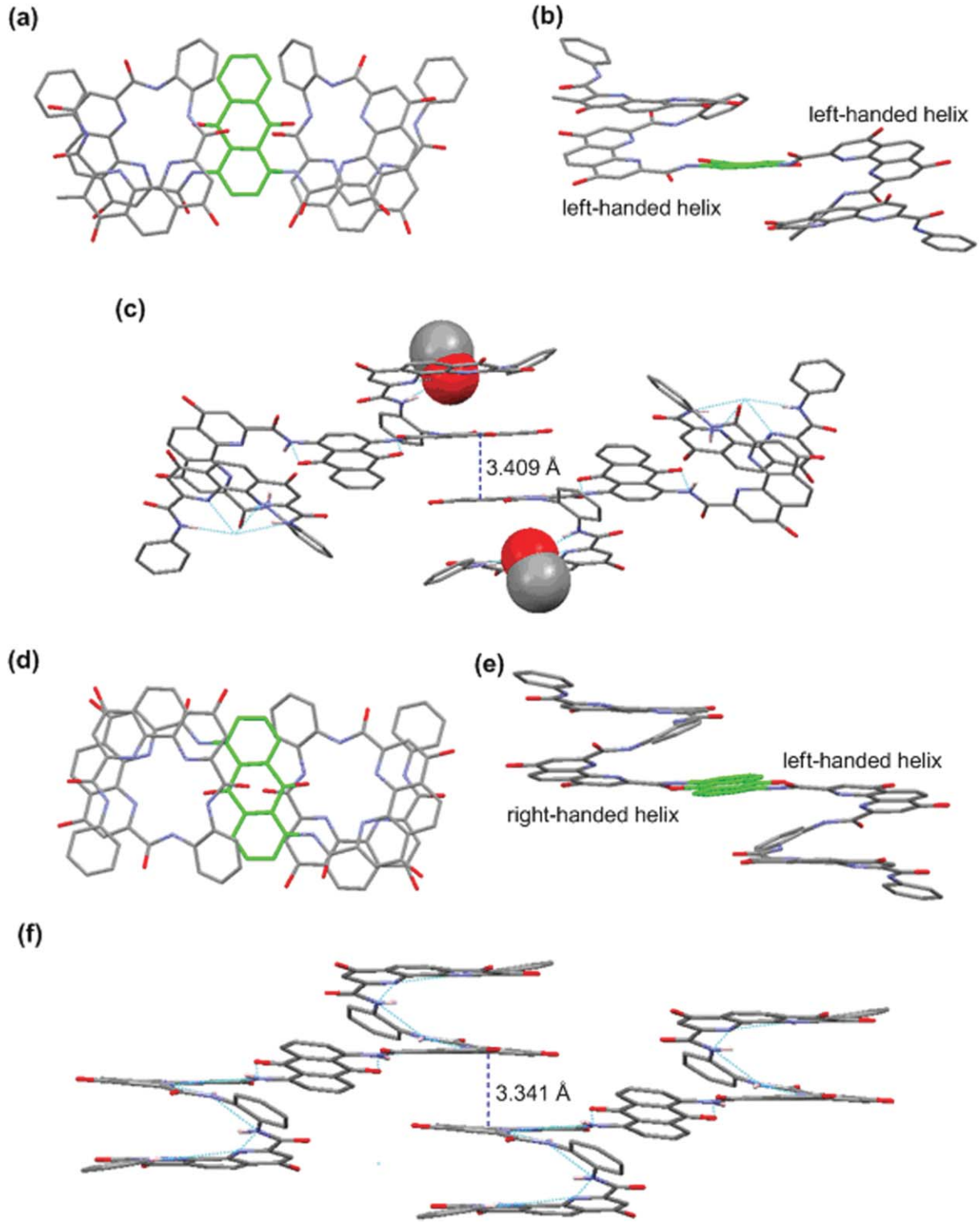


Fig. 4 Crystal structures of **2** (a) top view, (b) side view and (c) crystal packing (along an axis) with methanol molecules presented at the ends of the helix, and **4** (d) top view, (e) side view and (f) crystal packing (along an axis). Isobutyl chains and hydrogen atoms are omitted for clarity.

composed of two canonical helical secondary structures based on oligo(phenanthroline dicarboxamide) strands and diaminoanthraquinones inserted as the linkers. The very well defined supersecondary structures have been demonstrated by the UV/Vis, NMR spectra, and X-ray crystal analysis. Conformational investigations suggested that the aromatic linkers and their steric hindrance could control the relative orientation and handedness of two folded helical oligomers easily. The results presented here would offer a useful route for the *de novo* design of aromatic oligoamide foldamers with distinctive structural architectures.

Future work will be focused on the new highly organized artificial structures based on the oligo(phenanthroline dicarboxamide) helical foldamers, and their potential applications in asymmetric catalysis and materials science.

Experimental

General method for the synthesis of oligomers 1–6

To a solution of the diaminoanthraquinone **10** or **11** (1.19 g, 0.5 mmol) in CH_2Cl_2 (50 mL) was added the corresponding acid (1.5 mmol), 1-hydroxylbenzotriazole (HOBt) (230 mg, 1.5 mmol), and DCC (309 mg, 1.5 mmol). The reaction mixture was stirred at room temperature, and then refluxed for about 2 weeks. The precipitates were removed by filtration through Celite. The solution was concentrated, and the residue was washed with MeOH. The solid was purified by silica-gel column chromatography (ethyl acetate–dichloromethane–petrol ether 1 : 2 : 3) to give the product as an orange solid.

Compound 1. Yield: 91%. Mp >300 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): 14.21 (s, 2H, N*H*), 10.50 (bs, 2H, N*H*), 9.60 (s, 2H), 8.41–8.37 (m, 4H), 8.23 (bs, 2H), 8.12 (s, 2H), 7.66–7.60 (m, 6H), 6.94–6.93 (m, 4H), 6.84 (bs, 4H), 6.62 (bs, 2H), 4.27–4.21 (m, 8H, -OCH_2CH(CH_3)$_2$), 2.42–2.35 (m, 4H, -CH_2CH(CH_3)$_2$), 1.22–1.21 (m, -CH_2CH(CH_3)$_2$, 24H). ^{13}C NMR ($CDCl_3$, 150 MHz): 188.1, 165.0, 163.5, 151.7, 151.4, 145.7, 138.1, 137.7, 133.5, 132.4, 129.7, 128.4, 127.0, 124.4, 123.2, 123.0, 120.9, 120.7, 119.8, 102.3, 75.7, 28.4, 19.5. MALDI TOF MS: *m*/*z* 1178 [M + H]$^+$. Anal. Calcd. for $C_{70}H_{64}N_8O_{10}$: C, 71.41; H, 5.48; N, 9.52. Found: C, 71.22; H, 5.57; N, 9.36%.

Compound 2. Yield: 93%. Mp 296–298 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): 14.09 (s, 2H, N*H*), 11.61 (s, 2H, N*H*), 11.36 (s, 2H, N*H*), 11.61 (bs, 2H, N*H*), 9.36 (s, 2H), 8.38 (d, 2H, J = 9.1 Hz), 8.26–8.24 (m, 4H), 8.15 (d, J = 9.1 Hz, 2H), 8.06 (bs, 2H), 7.77–7.52 (m, 16H), 7.31 (bs, 2H), 7.20 (bs, 4H), 7.06 (t, 2H, J = 6.7 Hz), 6.98–6.91 (m, 4H), 4.15–4.02 (m, 12H, -OCH_2CH(CH_3)$_2$), 3.54 (bs, 4H, -OCH_2CH(CH_3)$_2$), 2.40–2.17 (m, 8H, -OCH_2CH(CH_3)$_2$), 1.23–1.11 (m, -OCH_2CH(CH_3)$_2$, 48H).^{13}C NMR ($CDCl_3$, 150 MHz): 188.1, 164.1, 163.5, 163.3, 163.2, 162.7, 162.6, 161.9, 151.4, 151.3, 150.6, 150.2, 145.4, 145.3, 145.2, 145.0, 137.9, 137.5, 134.3, 132.2, 130.3, 129.0, 128.3, 126.5, 125.8, 124.1, 123.0, 122.8, 122.4, 121.1, 120.2, 119.8, 102.3, 101.6, 75.6, 75.5, 75.4, 74.7, 39.1, 38.9, 34.3, 32.9, 32.0, 29.8, 29.6, 29.4, 29.2, 28.5, 28.4, 28.1, 23.1, 22.85, 22.82, 20.3, 19.5, 19.4, 19.3, 14.6, 14.33, 14.28, 11.6. MALDI TOF MS: *m*/*z* 2169 [M + Na]$^+$. Anal. Calcd. for $C_{126}H_{120}N_{16}O_{18}$·$2H_2O$: C, 69.34; H, 5.73; N, 10.27. Found: C, 69.56; H, 5.93; N, 9.85%.

Compound 3. Yield: 84%. Mp >300 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): 13.56 (bs, 2H, N*H*), 11.14–10.11 (m, 10H, N*H*), 8.83–6.19 (m, 56H), 4.03–3.61 (m, 24H, -OCH_2CH(CH_3)$_2$), 2.33–1.96 (m, 12H, -OCH_2CH(CH_3)$_2$), 1.25–0.87 (m, -OCH_2CH(CH_3)$_2$, 72H). ^{13}C NMR ($CDCl_3$, 150 MHz): 163.4, 163.3, 163.0, 162.9, 162.8, 162.7, 162.5, 162.3, 162.2, 162.10, 162.06, 162.0, 161.9, 161.8, 161.70, 161.66, 161.6, 161.5, 160.7, 151.1, 151.0, 150.9, 150.3, 150.2, 150.1, 150.0, 149.94, 149.89, 149.82, 149.7, 149.6, 145.3, 145.2, 145.1, 145.10, 145.05, 144.8, 144.5, 138.0, 137.1, 131.4, 130.3, 128.9, 128.6, 126.2, 125.8, 125.3, 125.2, 124.5, 124.4, 124.3, 124.0, 123.3, 123.1, 122.8, 122.3, 122.2, 122.10, 122.05, 121.6, 120.8, 120.4, 120.3, 120.2, 120.1, 102.2, 101.6, 101.4, 101.3, 101.2, 101.1, 101.0, 100.89, 100.85, 100.8, 100.7, 100.6, 100.5, 75.5, 75.4, 75.1, 75.0, 74.8, 74.7, 28.6, 28.5, 28.3, 28.2, 28.1, 19.8, 19.5, 19.4, 19.3, 19.0, 18.9. MALDI TOF MS: *m*/*z* 3116 [M + H]$^+$. Anal. Calcd. for $C_{182}H_{176}N_{24}O_{26}$·$2H_2O$: C, 69.36; H, 5.76; N, 10.67. Found: C, 69.40; H, 5.76; N, 10.59%.

Compound 4. Yield: 98%. Mp >300 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): 14.60 (s, 2H, N*H*), 11.37 (bs, 2H, N*H*), 9.17 (s, 2H, J = 8.3 Hz), 8.42–8.38 (m, 4H), 8.11 (s, 2H), 7.73–7.69 (m, 6H), 7.30 (t, 2H, J = 7.9 Hz), 7.02 (bs, 4H), 6.81 bs, 2H), 4.32–4.22 (m, 8H, -OCH_2CH(CH_3)$_2$), 2.43–2.36 (m, 4H, -OCH_2CH(CH_3)$_2$), 1.24–1.22 (m, -OCH_2CH(CH_3)$_2$, 24H). ^{13}C NMR ($CDCl_3$, 150 MHz): 187.7, 164.6, 163.5, 151.3, 140.4, 137.5, 135.5, 134.6, 128.3, 126.2, 124.6, 123.8, 123.2, 123.0, 121.5, 121.0, 120.7, 118.1, 102.2, 96.1, 75.6, 28.3, 19.3. MALDI TOF MS: *m*/*z* 1200 [M + Na]$^+$. Anal. Calcd. for $C_{70}H_{64}N_8O_{10}$·H_2O: C, 70.34; H, 5.57; N, 9.37. Found: C, 70.44; H, 5.59; N, 9.48%.

Compound 5. Yield: 96%. Mp >300 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): 13.38 (bs, 2H, N*H*), 11.60 (s, 2H, N*H*), 11.39 (bs, 2H, N*H*), 11.00 (bs, 2H, N*H*), 9.02 (bs, 2H), 8.33 (d, 2H, J = 9.0 Hz), 8.24 (bs, 4H), 8.18 (d, J = 9.0 Hz, 2H), 7.79–7.50 (m, 20H), 7.20 (bs, 4H), 7.31 (bs, 2H), 7.05 (bs, 4H), 6.96 (t, 2H, J = 7.3 Hz), 4.24–4.36 (m, 16H, -OCH_2CH(CH_3)$_2$), 2.40–2.16 (m, 8H, -OCH_2CH(CH_3)$_2$), 1.23–1.09 (m, -OCH_2CH(CH_3)$_2$, 48H). ^{13}C NMR ($CDCl_3$, 150 MHz): 164.0, 163.6, 163.3, 163.2, 162.8, 162.7, 151.4, 151.3, 150.4, 145.43, 145.35, 145.25, 145.18, 145.13, 145.09, 140.2, 138.0, 134.6, 130.2, 128.9, 126.12, 126.09, 125.2, 124.3, 124.2, 123.4, 122.9, 122.52, 122.47, 122.42, 122.40, 121.05, 121.02, 120.99, 120.44, 120.40, 120.33, 120.31, 120.2, 118.3, 102.3, 101.7, 101.63, 101.60, 75.6, 75.4, 74.8, 28.5, 28.42, 28.39, 19.49, 19.45. MALDI TOF MS: *m*/*z* 2169 [M + Na]$^+$. Anal. Calcd. for $C_{126}H_{120}N_{16}O_{18}$: C, 70.51; H, 5.64; N, 10.44. Found: C, 70.42; H, 5.72; N, 10.38%.

Compound 6. Yield: 89%. Mp >300 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): 13.06 (bs, 2H, N*H*), 11.04–9.76 (m, 10H, N*H*), 8.30–6.49 (m, 56H), 4.05–3.61 (m, 24H, -OCH_2CH(CH_3)$_2$), 2.35–2.06 (m, 12H, -OCH_2CH(CH_3)$_2$), 1.25–1.00 (m, -OCH_2CH(CH_3)$_2$, 72H). ^{13}C NMR ($CDCl_3$, 150 MHz): 164.1, 164.0, 163.8, 163.6, 163.5, 163.4, 163.42, 163.35, 163.2, 163.0, 162.7, 162.5, 162.4, 162.3, 162.2, 162.04, 161.98, 161.91, 161.87, 161.7, 161.43, 161.36, 161.3, 151.7, 151.5, 151.4, 151.3, 150.9, 150.8, 150.7, 150.6, 150.5, 150.43, 150.39, 150.3, 150.2, 150.2, 150.1, 150.0, 149.9, 149.8, 149.6, 149.5, 149.44, 149.38, 145.36, 145.3, 145.0, 144.8, 144.4, 139.4, 139.35, 139.30, 138.1, 134.0, 133.8, 133.6, 130.7, 128.8, 125.6, 124.0, 123.2, 122.8, 122.5, 122.3, 122.1, 121.3, 120.8, 120.4, 120.3, 120.1, 119.8, 119.7, 119.6, 117.85, 117.79, 102.1, 101.82, 101.76, 101.7, 101.6, 101.4, 101.32, 101.26, 101.1, 101.0, 100.9, 100.8, 100.7, 100.6, 100.5, 100.4, 100.3, 100.24, 100.20, 100.1, 75.5, 75.0, 29.9, 28.4, 28.3, 28.1, 27.9, 19.8, 19.5, 19.4, 19.3, 18.8. MALDI TOF MS: *m*/*z* 3138 [M + Na]$^+$. Anal. Calcd. For $C_{182}H_{176}N_{24}O_{26}$·$H_2O$: C, 69.76; H, 5.73; N, 10.73. Found: C, 69.63; H, 5.84; N, 10.62%.

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