Tetrahedron 65 (2009) 9494–9504

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Hydrogen bonded aromatic hydrazide foldamers for the self-assembly of vesicles and gels

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ARTICLE INFO

Article history:
Received 27 May 2009
Received in revised form 22 July 2009
Accepted 23 July 2009
Available online 11 September 2009

Keywords:
Foldamer
Hydrogen bonding
Hydrazide
Vesicles
Organogels
Self-assembly

ABSTRACT

This paper describes an investigation of the structural and side-chain factors for the formation of vesicles and gels by hydrogen bonding-mediated aromatic hydrazide foldamers. Six foldamers and one straight analog that bear discrete side chains have been synthesized. SEM and AFM studies reveal that the molecules with the appended 2-(2-(dialkyl-amino)-2-oxoethylamino)-2-oxoethoxyl chains form vesicles, hydrogels or organogels, depending on the solvents. Both the inner amide units and the terminal *N*,*N*-dialkylamide units in the chains are revealed to play essential roles in controlling the self-assembly. The former facilitates it by forming the intermolecular hydrogen bonding, while the latter modulates it by providing solubility and balancing the hydrophobicity of the whole molecules in solvents of varying polarity.

1. Introduction

Vesicles are membrane-enclosed sacs at the nano to micro scales, which have found wide applications in studies in biomimetics, nanomaterials, and drug and gene delivery.[1] Inspired by the formation of biomembranes from amphiphilic phospholipids, chemists have developed an ocean of amphiphilic molecular and macro-molecular structures that spontaneously form vesicular structures.[2–5] However, the design of non-amphiphilic structures for the formation of vesicles has been a great challenge.[6] Organogels are another family of assembled structures in which a gelator immobilizes a solvent by forming a three-dimensional entangled network.[7] In the past two decades, the development of molecular and supramolecular gels has received considerable attention due to their potential usefulness in studies in discrete functional materials.[8] Since both vesicles and gels are formed dynamically in the bottom-up manner, several surfactants and amphiphilic polymers have been revealed to selectively generate both of them by modulating the assembling conditions such as pH value, concentration, and temperature.[9,10]

We previously reported a class of aromatic hydrazide-based foldamers, the folded conformations of which are stabilized by the intramolecular three-center hydrogen bonding.[11,12] More recently, we found that this class of folded frameworks is capable of forming vesicles in methanol and gelating hydrocarbons such as *n*-hexane, cyclohexane, *n*-heptane, *n*-octane, and *n*-decane.[13] Instead of using the hydrophobic alkyl groups or hydrophilic oligoglycol groups that are widely used to tune the amphiphilicity of other rigid aromatic segments,[6,14] we developed a new hybrid aliphatic chain, i.e., the 2-(2-(dioctylamino)-2-oxoethylamino)-2-oxoethoxyl unit, to facilitate the formation of the new three-dimensional entities. To systematically explore the structural factors that regulate the selective formation of the two kinds of three-dimensional architectures, we have designed and synthesized seven new preorganized analogs with discrete side chains or backbones. SEM and AFM investigations reveal that these compounds are capable of selectively forming vesicles and hydrogels in aqueous methanol and organogels in apolar hydrocarbons, which are reported in this paper.

2. Results and discussion

2.1. Design and synthesis

Compound **1** has been revealed to form vesicles in methanol.[13] To investigate the effects of the amide and alkyl units of the side chains on the self-assembly, compounds **2**, **3**, and **4a**–**d** were synthesized. Compound **5** was also prepared. A comparison of its assembling behavior with that of **4c** would reveal the effect of the shape of the backbones.

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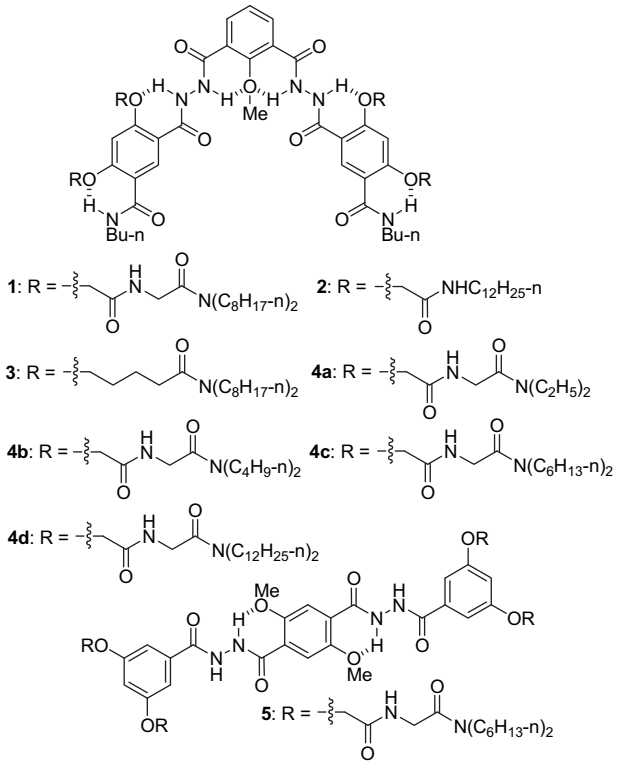
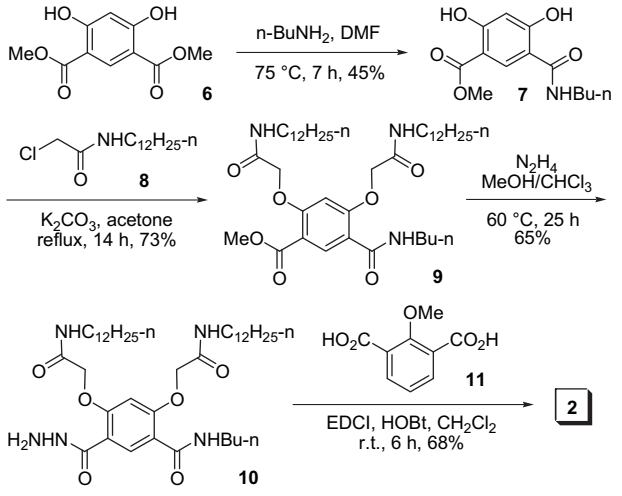
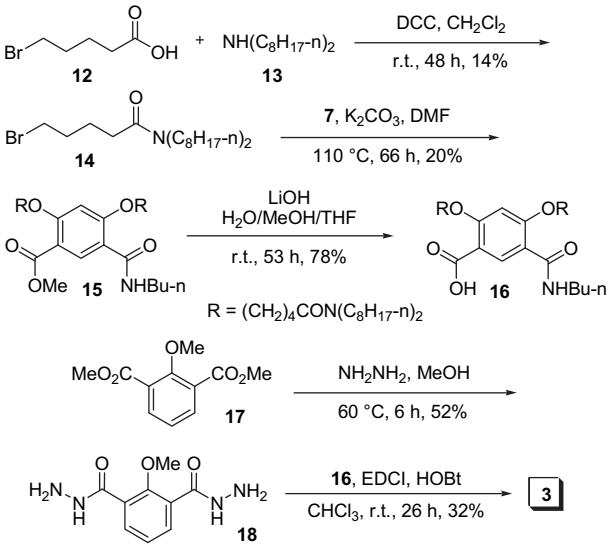
0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.07.097



The synthesis of **2** is shown in Scheme 1. Compound **6** was first treated with *n*-butylamine in DMF to give **7** in 45% yield. The latter was then reacted with **8** in acetone in the presence of potassium carbonate to afford **9** in 73% yield. Treatment of **9** with hydrazine in refluxed methanol and chloroform produced **10** in 65% yield. Finally, the coupling reaction of **10** with **11** in dichloromethane in the presence of EDCI and HOBt gave **2** in 68% yield. For the synthesis of **3** (Scheme 2), amide **14** was first obtained from the coupling of **12** and **13**. Treatment of **15** with **14** in hot DMF in the presence of potassium carbonate gave rise to **15** in 20% yield. Hydrolysis of **15** with lithium hydroxide in aqueous methanol and THF generated acid **16** in 78% yield. With **16** available, compound **18** was prepared in 52% from the reaction of **17** and hydrazine in refluxed methanol. The coupling reaction of **18** with **16** in chloroform in the presence of EDCI and HOBt produced **3** in 32% yield.

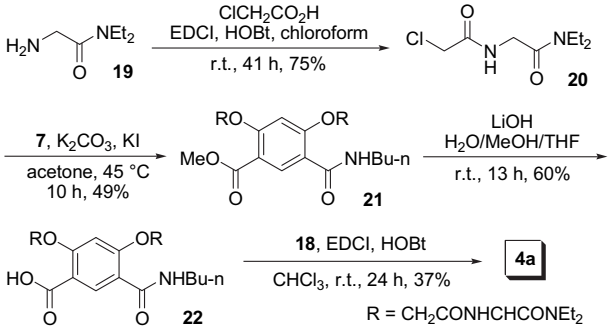


Scheme 1. The synthetic route for compound **2**.



Scheme 2. The synthetic route for compound **3**.

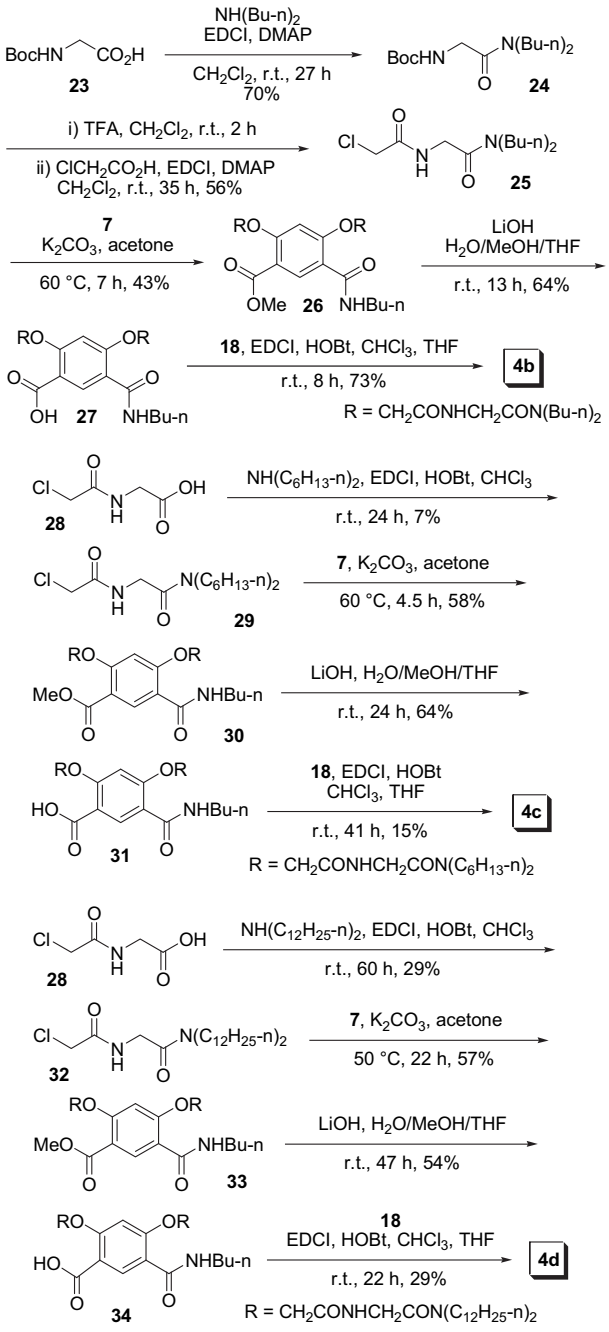
For the synthesis of **4a** (Scheme 3), **19** was first coupled with chloroacetic acid to give **20** in 75% yield. The latter was then reacted with **7** in acetone in the presence of potassium carbonate to give **21** in 49% yield. This ester was hydrolyzed with lithium hydroxide to **22**, which was then coupled with **18** to give **4a** in 37% yield. Compounds **4b**–**d** and **5** were prepared by using the similar procedures and the detailed routes are shown in Schemes 4 and 5.



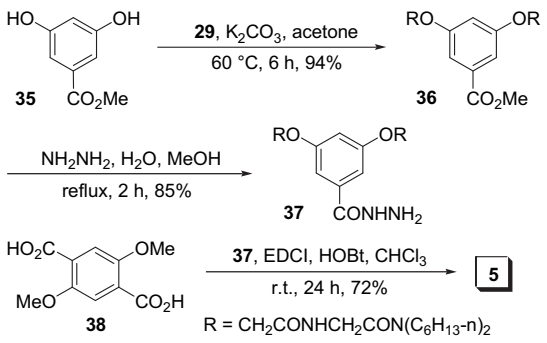
Scheme 3. The synthetic route for compound **4a**.

2.2. Self-assembly in methanol

The capacity of compounds **2**, **3**, **4a**–**d**, and **5** of forming vesicles in methanol was first investigated by SEM. Compound **2** did not dissolve in methanol, suggesting that the terminal *N*,*N*-dialkylamide units in the side chains in **1** was essential in providing the solubility in methanol. The SEM image of **3** showed that it mainly formed membrane-like structures, together with some vesicles (Fig. 1a), indicating that the inner amide units in the side chains also contributed significantly to the formation of the vesicles through the intermolecular C=O···H–N hydrogen bonding,[13] which was expected not only to enhance the stacking of the backbones, but also to increase the directionality of the stacking. Compounds **4a**–**d** all gave rise to vesicles (Fig. 1b–e). The size of the vesicles formed by **4a** was considerably smaller than those of **4b**–**d**. Moreover, its vesicles preferred to fuse to generate aggregates of twins, triplets or quadruplets. Although aggregation was also observed for the vesicles of **4c** and **4d**, only the membranes of the contacting parts of the vesicles of **4a** were broken, suggesting that these vesicles fused to form new single entities. In contrast, the aggregated vesicles of **4c** and **4d** kept their boundaries, indicating that the contacted membranes of the vesicles did not break



Scheme 4. The synthetic routes for compounds **4b**–**d**.



Scheme 5. The synthetic route for compound **5**.

completely. This difference should be caused by the terminal alkyl groups in the chains. Previous study established that this family of vesicles has a one-layered structure.[13] The ethyl groups of **4a** are small and the whole chain should act mainly as a polar unit. Therefore, the contacting parts could fuse through the rearrangement of the stacked backbones. In contrast, the long hexyl and dodecyl groups of **4c** and **4d** are quite hydrophobic, which were expected to entangle along the cylinders of the stacked backbones and thus to form a hydrophobic layer on the outside of the stacked cylinders to inhibit the fusion of the stacked backbones. The straight trimer **5** also formed vesicles (Fig. 1f), but their average sizes were remarkably smaller than those of **4c**. Because the measurements were carried out under the identical condition, this result suggested that the shape of the backbones also imposed an important influence on the formation of the vesicles.

AFM images further supported the formation of the vesicular structures by **3**, **4a**–**d**, and **5**. The representative results are shown in Figure 2. Different from the SEM result (Fig. 1a), no membrane-like entities were observed for **3** under this lower concentration. The sizes of the vesicles were generally smaller than the related ones in Figure 1, because the concentrations of the samples were decreased. The smaller vesicles did not aggregate, possibly due to the decrease of their density. The ratios of the diameter and height were generally >4, which further evidenced that they were hollow and became flattened upon being transferred from solution to the mica surface. The ratio values of **4b** and **4c** (averagely 4–5) were notably smaller than those of others (averagely >10), implying that the vesicles formed by these two compounds were more stable and therefore collapsed to a smaller extent upon evaporation of the entrapped solvent. TEM images also showed that the above compounds assembled into vesicular structures in methanol. As examples, the results of **4a** and **4b** are presented in Figure 2.

2.3. Self-assembly in methanol–water mixtures

The above results indicated that the new aliphatic chains are efficient in promoting the formation of the vesicles. Owing to the increased hydrophilicity of the chains with short terminal alkyl groups, compounds **4a**–**c** were soluble in methanol–water mixture and **4a** was even soluble in pure water. Their assembling behaviors in the binary solvents were then investigated. Figure 3 presents the SEM images of **4a** (4 mM), which revealed that, depending on the content of water, it could self-assemble into monolayer vesicles, hydrogels, and multilayer vesicles. The compound selectively formed vesicles in pure methanol. With the addition of water, both vesicles and fibrils were formed simultaneously (Fig. 3a), reminiscent of the orthogonal self-assembly of two different components into two types of supramolecular entities in a single system.[15] These two forms of three-dimensional structures co-existed until water was increased to 30%. When water was increased to 60%, long thick fibers were formed selectively (Fig. 3c). Interestingly, extended membranes with cracks were also generated during this transition (Fig. 3b). When water content was in the range of ca. 50–80%, stable hydrogels were generated. For the solvent of 60% water, the lowest gelation concentration was about 2.7 mg/mL. With water content being further increased (80–100%), the mixture became transparent and flowing again. SEM images showed that both thin fibrils and spherical particles were generated. The spherical particles were hollow and open, implying that they were of multilayer structures (Fig. 3d, inset).[16]

The above result well illustrates the dynamic feature of the self-assembly of vesicles and hydrogels.[10] The key for the conversion of the vesicles of **4a** to the hydrogels should be that, upon increase of water, both the strength and directionality of the stacking of the backbones were increased. As a result, the formation of long stacking cylinders was favored, which further aggregated to generate entangled fibers to gelate the solvent (Fig. 4). Since the

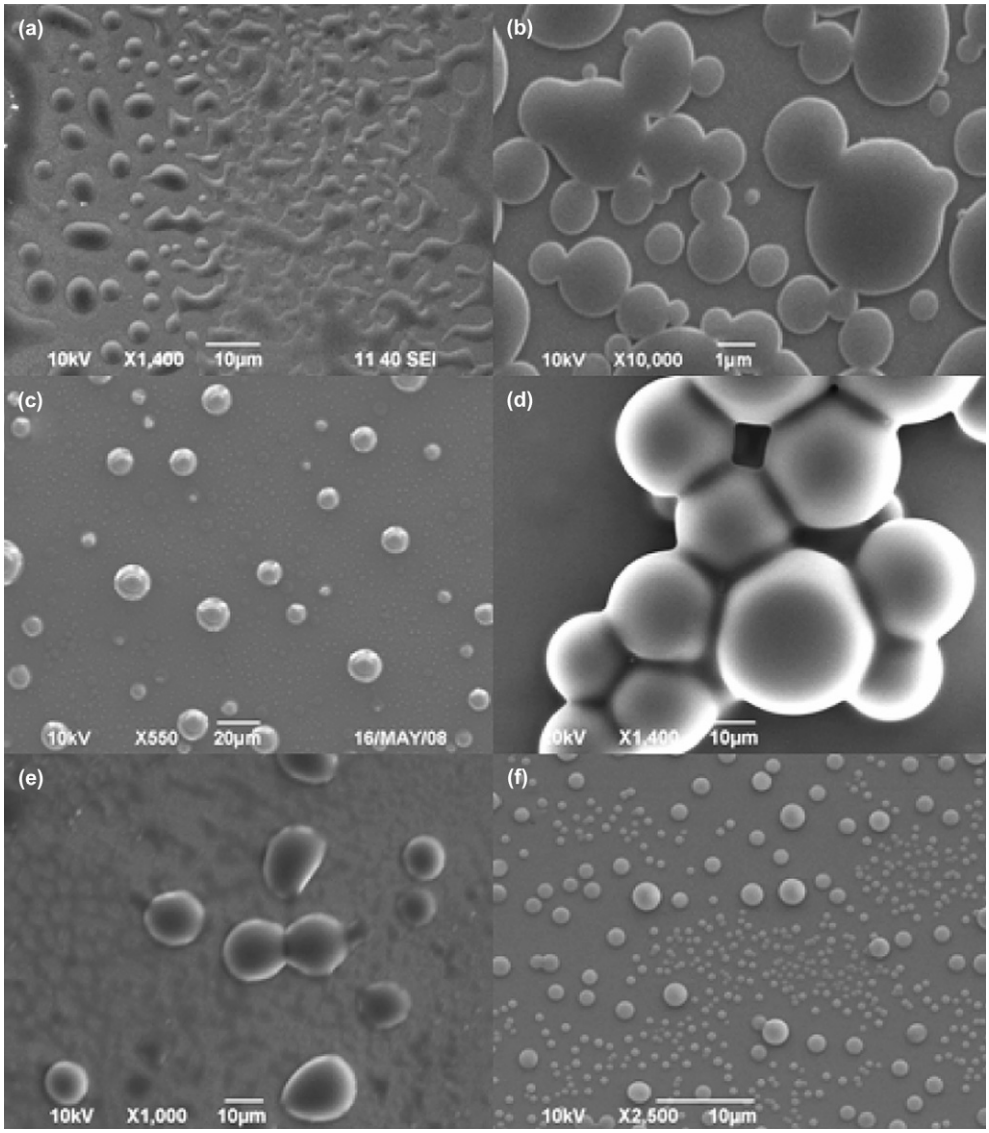


Figure 1. SEM images of the samples of (a) **3** (4 mM), (b) **4a** (4 mM), (c) **4b** (4 mM), (d) **4c** (4 mM), (e) **4d** (0.16 mM), and (f) **5** (0.45 mM) in methanol on mica surface, obtained upon evaporation of the solvent.

hydrogels could be generated by directly dissolving **4a** in the mixture solvent of high water content or by adding water to the solution of low water content, the fibers might be generated through the fusion of the vesicles or directly by the stacking of the single molecules. From all the SEM images, no linear fused aggregates of twins, triplets or multiplets were observed (vide infra). Therefore, it is reasonable to propose that the fibers of **4a** were formed mainly through the one-dimensional stacking of the single molecules (Fig. 4), which was facilitated by the increase of the solvent polarity with the increase of the water content.

The self-assembly of **4b** in the binary solvent was first investigated at 14 mM. The compound dissolved completely in methanol–water mixture when water content was <20% and partially dissolved when water content was 25–50%. Within this range of water content, it dissolved upon heating and formed hydrogels after cooling to room temperature. When water was further increased, it could not dissolve completely even at refluxing temperature and no hydrogels were formed. Figure 5 presents SEM images of the samples obtained by evaporating the solutions of varying water content. When water was less than 18%, only vesicles were observed, which aggregated increasingly with the addition of water (Fig. 5a). When water was increased from 18% to 30%, fibers were increasingly generated, while the density of vesicles was gradually reduced. Different from those of **4a**, the fibers of **4b** were obviously formed by the fusion of the vesicles (Fig. 4), because partially fused and necklace-like fibrils were clearly exhibited in the transition area (Fig. 5b–d). When water was 30–50%, hydrogels were formed upon cooling the hot solution. The lowest gelation concentration was 3.0 mg/mL for the system of 40% water. SEM images showed that fibrous structures were formed exclusively, which became thicker and further aggregated to form band-styled fibers with the increase of water content (Fig. 5e). The hydrogels could also be formed at lower concentration without heating. For example, the solution of 30% water at 4 mM turned into a hydrogel after standing for 1 h. Interestingly, in addition to the fibrous structures, conical objects were also observed on the SEM image under this condition (Fig. 5f),[17] although their detailed formation mechanism has not been clarified. Adding methanol to the gels of high water content could dissolve the gels. SEM images obtained from the resulting transparent solution showed that vesicles were formed exclusively, again reflecting the reversible feature of the assembling process.

Compound **4c** had a solubility of 4 mM in the binary solvent of 10% water. SEM images showed that it formed vesicles in this solvent. Further increasing water content dramatically reduced the

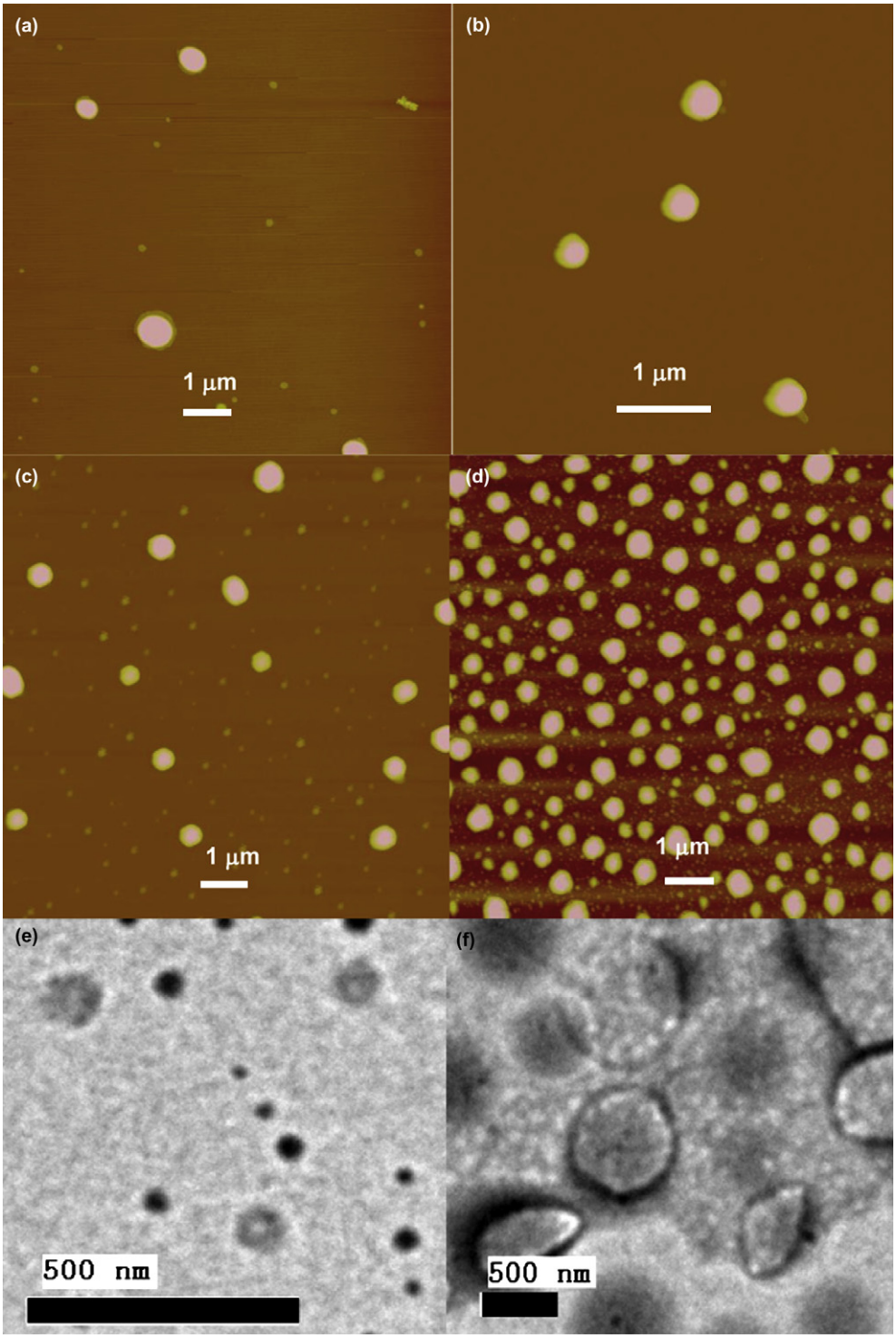


Figure 2. Tapping-mode AFM images of (a) **3**, (b) **4b**, (c) **4c**, and (d) **4d**, obtained by evaporation of their methanol solution (0.05 mM). TEM images of (e) **4a** and (f) **4b**, obtained by evaporation of their methanol solution (0.5 mM).

solubility. Possibly owing to the low solubility, **4c** did not gelate the binary solvent of any ratio. SEM images also showed that no fibrils were generated in all the investigated binary solvents. The result indicated that, with the elongation of the terminal alkyl groups in the chains, the hydrophilicity of the molecules was decreased substantially, disabling the formation of long stacking entities in more polar solvent. The solubility of **4d** was low in methanol and reduced very quickly with the addition of water. Similar to **4c**, it did not form fibrous structures in any water and methanol mixture.

2.4. Self-assembly in hydrocarbons

Compounds **4c** and **4d** have longer terminal aliphatic chains and are therefore more hydrophobic. Their assembling properties in apolar hydrocarbons were also investigated. Compound **4c** was insoluble in linear alkanes, including *n*-hexane, *n*-heptane, and *n*-octane, but able to gelate cyclic molecules such as cyclohexane, decalin, tetralin, and toluene. The lowest gelation concentration was 20, 25, 150, and 160 mg/mL, respectively. The latter two values

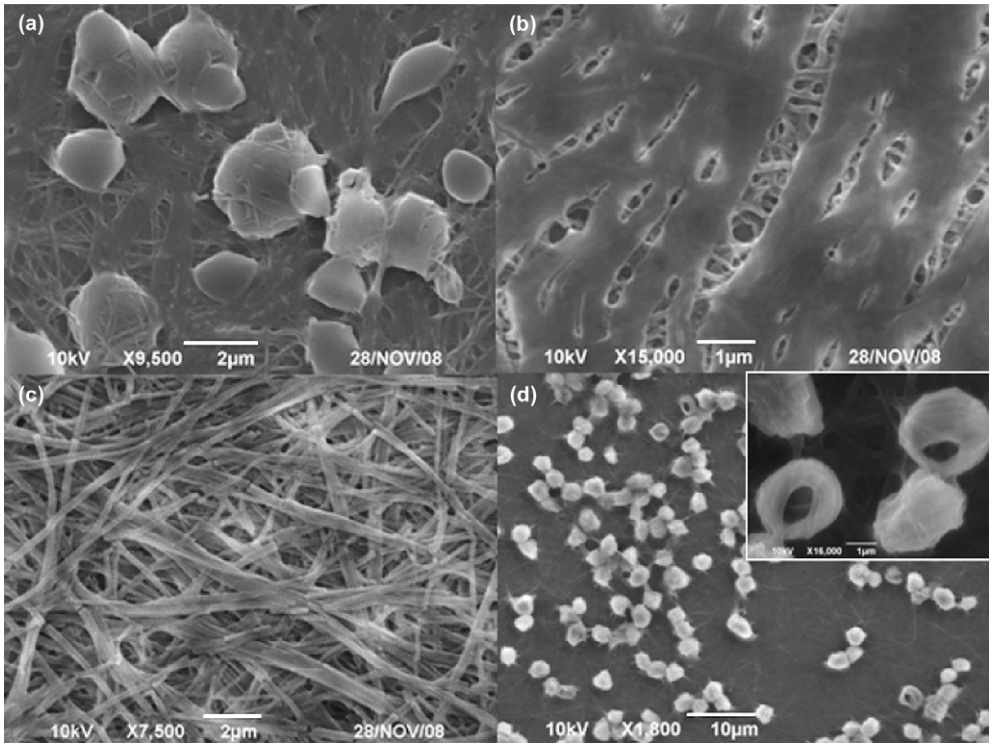


Figure 3. SEM images of the samples of **4a** (4 mM) obtained by evaporating the solution of methanol and water on mica surface. The content of water (v/v%) is (a) 20%, (b) 40%, (c) 60%, and (d) 100% (inset: the bar is 1 μm).

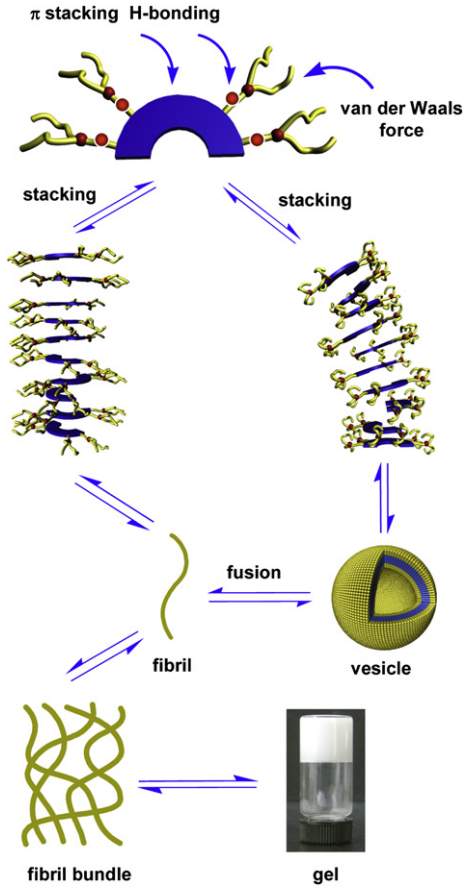


Figure 4. Model for the self-assembly of vesicles and (hydro)gels by compounds **4a**–**d** in aqueous methanol and hydrocarbons.

were considerably higher than the former two, which may be attributed to the competitive stacking interaction of the benzene ring of tetralin and toluene, which weakened the stacking of the backbones of **4c**. Compound **4d** was of good solubility in all the above four solvents, but able to gelate linear hydrocarbons, including *n*-hexane, *n*-heptane, and *n*-octane. The lowest gelation concentration was 156, 108, and 92 mg/mL, respectively. Since compound **1** has been revealed to gelate *n*-hexane, *n*-heptane, *n*-octane, and cyclohexane,[13] these results appeared to indicate that foldamers with longer terminal alkyl chains possess relative large capacity of gelating linear alkanes, which may be rationalized by considering the better structural matching between the long alkyl chains and the solvent molecules.

The AFM images obtained for the solutions of compounds **4c** and **4d** in the hydrocarbons exhibited less ordered membrane-like fibrils (Fig. 6). In these apolar solvents, the intermolecular hydrogen bonding formed by the amides of the side chains should be strengthened. Therefore, this result should be ascribed to the weakening of the stacking interaction of their rigid frameworks. In the apolar solvents, the terminal alkyl groups of different stacking cylinders may also interact to a greater extent, which may also promote the formation of such membrane-like fibrils. SEM images also showed that **4c** and **4d** formed cotton-like fibrils or even membranes (Fig. 6c), again reflecting the less ordering of the stacking of the molecules.

3. Conclusions

In this study, we describe a systematic study of the self-assembly of hydrogen bonding preorganized aromatic hydrazide derivatives that bear multiple 2-(2-(dialkyl-amino)-2-oxoethylamino)-2-oxoethoxyl side chains. We demonstrate that molecules of this series are robust in forming vesicles, hydrogels or organogels in both polar and apolar solvents, which are regulated by the sizes of the terminal alkyl groups. The result illustrates the versatility of the new

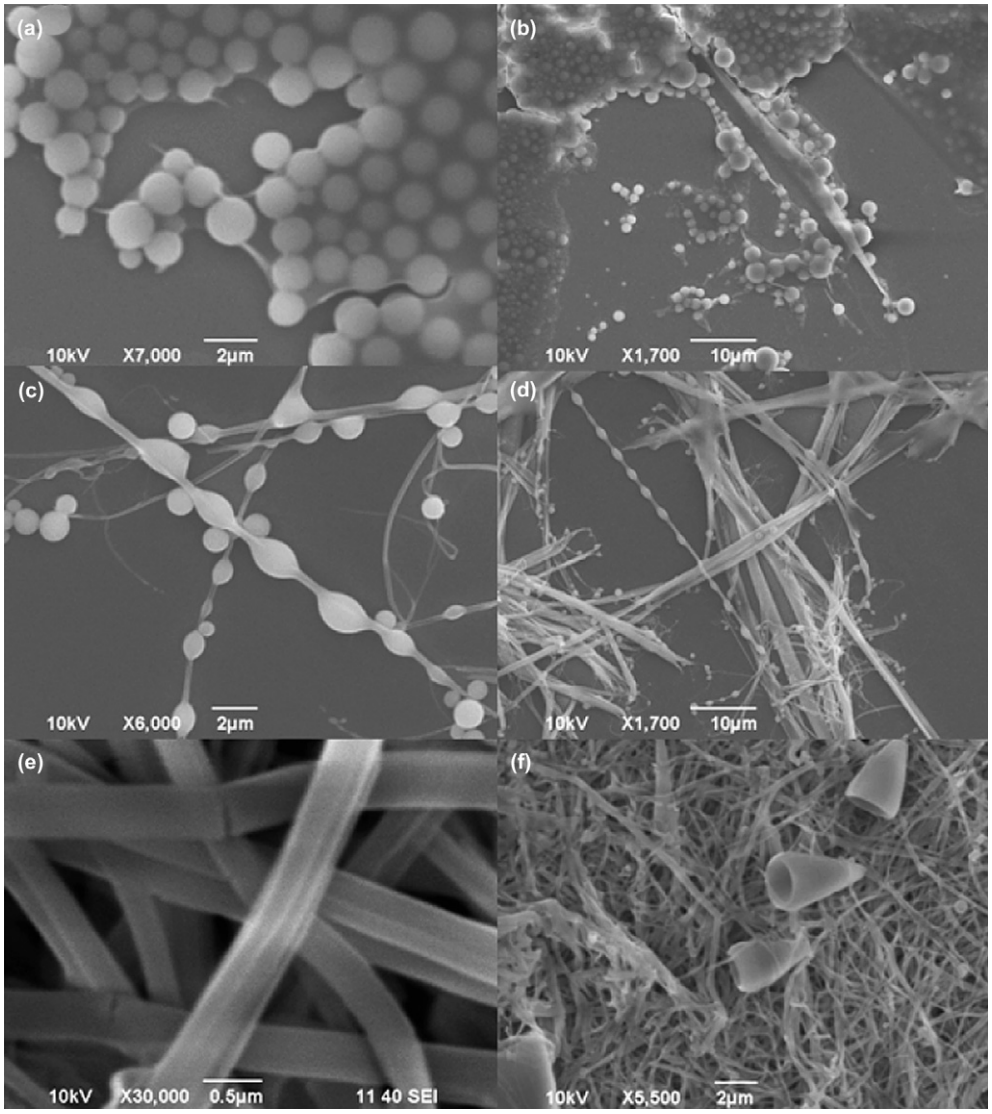


Figure 5. SEM images of the sample of **4b** (14 mM) obtained by evaporating the methanol–water mixture on mica surface. The content of water (v/v%) was (a) 18% (solution), (b) 20% (solution), (c) 24% (solution), (d) 26% (solution), (e) 50% (cooling the hot solution, hydrogel), and (f) 30% (4 mM, hydrogel without heating).

amide–alkyl hybrid chains in modulating the hydrophilicity and hydrophobicity of the assembling components. Since the backbones impose an important influence on the assembling outcome, we may expect that other rigid aromatic backbones can be constructed for assembling new ordered functional architectures. Because the folded framework is planar and large in size, as the next step, we will design hydrophobic cyclophanes to test the possibility of transmembrane exchange by embedding them in the membranes of the vesicles through stacking interaction.

4. Experimental section

4.1. General methods

See Ref. 13.

4.1.1. Compound **7**. A solution of **6** (5.00 g, 22.1 mmol) and *n*-butylamine (2.40 g, 33.0 mmol) in DMF (25 mL) was stirred at 75 °C for 7 h and then concentrated. The resulting residue was dissolved in CH_2Cl_2 (60 mL) and the solution washed successively with water (30 mL), hydrochloric acid (1 N, 20 mL), and brine (20 mL) and dried over sodium sulfate. Upon removal of the solvent, the crude product was purified by column chromatography (acetone/PE 1:10) to give **7** as a white solid (2.70 g, 45%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=13.20 (s, 1H), 11.06 (s, 1H), 7.92 (s, 1H), 6.48 (s, 1H), 6.22 (br, 1H), 3.94 (s, 3H), 3.47–3.41 (m, 2H), 1.67–1.57 (m, 2H), 1.48–1.35 (m, 2H), 0.97 (t, J=7.2, 7.2 Hz, 3H). MS (ESI): m/z 266.1 $[M-H]^-$.

4.1.2. Compound **9**. A suspension of **7** (0.30 g, 1.10 mmol) and K_2CO_3 (1.00 g, 7.20 mmol) in acetone (50 mL) was stirred for 1 h and then **8** (0.60 g, 2.30 mmol) and KI (70 mg, 0.42 mmol) added. The mixture was heated at 60 °C for 14 h and then cooled. The solid was filtrated off and the filtrate concentrated in vacuo. The resulting residue was dissolved in CH_2Cl_2 (50 mL) and the solution washed with aqueous HCl (1 N, 50 mL), brine (30 mL) and dried over sodium sulfate. Upon removal of the solvent, the crude product was recrystallized from MeOH to give **9** as a white solid (0.58 g, 73%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.44 (s, 1H), 8.11 (br, 1H), 7.23 (br, 1H), 7.06 (br, 1H), 6.38 (s, 1H), 4.67 (s, 2H), 4.52 (s, 2H), 3.87 (s, 3H), 3.49–3.42 (m, 2H), 3.39–3.29 (m, 4H), 1.70–1.54 (m, 4H), 1.48–1.24 (m, 40H), 0.96 (t, J=7.2, 7.2 Hz, 3H), 0.87 (t, J=6.9, 6.9 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=167.0, 166.5, 164.7, 164.4, 160.9, 160.2, 135.3, 117.5, 112.4, 98.5, 68.1, 67.8, 51.9, 39.8, 39.4, 39.3, 31.8, 31.5, 29.6, 29.5, 29.4, 29.3, 29.2, 26.9, 22.6, 20.2, 14.0, 13.7. MS (ESI): m/z 718.4 $[M+H]^+$, 740.4 $[M+Na]^+$.

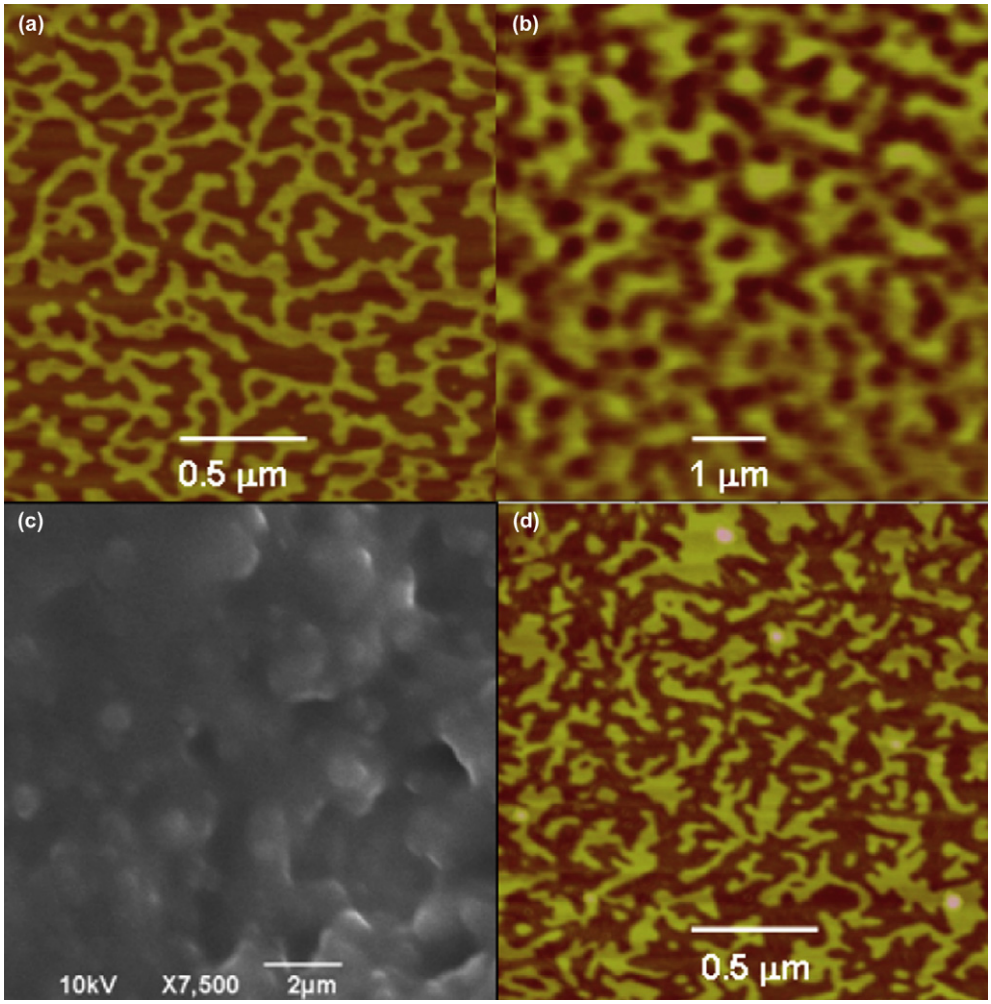


Figure 6. (a) AFM image of **4c** obtained from the toluene solution (0.05 mM), (b) AFM image of **4d** obtained from the *n*-hexane solution (0.05 mM), (c) SEM image of **4d** obtained from the *n*-hexane solution (0.1 mM), and (d) AFM image of **4d** obtained from the *n*-octane solution (0.05 mM).

Anal. Calcd for $C_{41}H_{71}N_3O_7$: C, 68.58; H, 9.97; N, 5.85. Found: C, 68.58; H, 10.55; N. 5.73.

4.1.3. Compound ***21***. ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.68 (s, 1H), 8.42 (s, 1H), 7.69 (s, 1H), 7.61 (s, 1H), 6.42 (s, 1H), 4.76 (s, 2H), 4.62 (s, 2H), 4.20 (d, J=5.1 Hz, 2H), 4.13 (d, J=4.5 Hz, 2H), 3.91 (s, 3H), 3.51–3.25 (m, 10H), 1.65–1.33 (m, 4H), 1.24–1.10 (m, 12H), 0.93 (t, J=7.2, 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=167.8, 167.0, 166.7, 165.0, 164.3, 160.8, 159.8, 137.1, 117.1, 113.6, 98.5, 68.1, 68.0, 52.3, 41.3, 41.1, 41.0, 40.8, 40.7, 40.0, 31.8, 20.5, 14.3, 14.2, 14.1, 13.2, 13.1. MS (ESI): m/z 608.3 $[M+H]^+$, 630.4 $[M+Na]^+$. HRMS (ESI): Calcd for $C_{29}H_{45}N_5O_9Na$ $[M+Na]^+$: 630.3110. Found: 630.3120.

4.1.4. Compound ***26***. ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.70 (s, 1H), 8.40 (s, 1H), 7.66 (s, 1H), 7.57 (s, 1H), 6.39 (s, 1H), 4.75 (s, 2H), 4.61 (s, 2H), 4.19 (d, J=4.5 Hz, 4H), 4.12 (d, J=4.5 Hz, 4H), 3.91 (s, 1H), 3.51–3.44 (m, 2H), 3.37–3.30 (m, 4H), 3.23–3.16 (m, 4H), 1.62–1.49 (m, 10H), 1.45–1.24 (m, 10H), 0.97–0.88 (m, 15H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=167.4, 167.1, 166.7, 166.5, 164.8, 163.9, 160.5, 159.5, 137.1, 116.9. 113.6, 98.2, 67.9, 67.8, 52.1, 46.8, 46.7, 46.0, 45.9, 40.8, 40.8, 39.8, 31.6, 30.8, 30.8, 29.7, 29.6, 20.2 (d), 20.1 (t), 13.8 (d). MS (ESI): m/z 720.3 $[M+H]^+$, 742.3 $[M+Na]^+$. Anal. Calcd for $C_{37}H_{61}N_5O_9$: C, 61.73; H, 8.54; N, 9.73. Found: C, 61.63; H, 8.45; N, 9.74.

4.1.5. Compound ***30***. ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.69 (s, 1H), 8.39 (t, J=4.8 Hz, 1H), 7.67 (t, J=4.8 Hz, 1H), 7.58 (t, J=3.6 Hz, 1H), 6.39 (s, 1H), 4.75 (s, 2H), 4.61 (s, 2H), 4.19 (d, J=4.8 Hz, 2H), 4.12 (d, J=3.6 Hz, 2H), 3.91 (s, 3H), 3.47 (q, J=6.9 Hz, 2H), 3.32 (q, J=7.2 Hz, 2H), 3.18 (q, J=6.9 Hz, 2H), 1.63–1.27 (m, 36H), 0.96–0.84 (m, 15H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=167.8, 167.3, 166.9, 165.0, 164.3, 160.7, 159.8, 137.2, 117.1, 113.5, 98.4, 68.1, 68.0, 52.3, 47.3, 47.2, 46.5, 46.4, 41.1, 41.0 (d), 31.8 (d), 31.7 (d), 31.7, 29.0, 28.9, 27.7, 26.9 (d), 26.8, 26.7, 22.8, 20.5, 14.2 (d), 14.0. MS (ESI): m/z 832.8 $[M+H]^+$, 854.7 $[M+Na]^+$. Anal. Calcd for $C_{45}H_{77}N_5O_9$: C, 64.95; H, 9.33; N, 8.42. Found: C, 64.88; H, 9.67; N, 8.36.

4.1.6. Compound ***33***. ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.72 (s, 1H), 8.39 (s, 1H), 7.64 (s, 1H), 7.53 (s, 1H), 6.38 (s, 1H), 4.74 (s, 2H), 4.62 (s, 2H), 4.19 (d, J=4.2 Hz, 2H), 4.13 (d, J=2.1 Hz, 2H), 3.92 (s, 3H), 3.52–3.16 (m, 10H), 1.58–1.35 (m, 10H), 1.42–1.31 (m, 4H), 1.26 (br, 72H), 0.96–0.85 (m, 15H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=167.7, 167.3, 166.9, 166.8, 165.0, 164.2, 160.8, 159.8, 137.3, 117.1, 113.7, 98.4, 68.1, 68.0, 52.4, 47.4, 47.3, 46.6, 46.5, 41.1, 41.0, 40.1, 32.1, 31.8, 29.9, 29.8 (d), 29.7, 29.6 (d), 29.5, 29.0 (d), 27.8, 27.3, 27.2, 27.1, 27.1, 22.9, 20.5, 14.3, 14.1. MS (MALDI-TOF): m/z 1170.0 $[M+H]^+$, 1191.3 $[M+Na]^+$. HRMS (MALDI-TOF): Calcd for $C_{69}H_{126}N_5O_9$: 1168.9550 $[M+H]^+$. Found: 1168.9548.

4.1.7. Compound ***10***. A solution of **9** (0.40 g, 0.56 mmol) and hydrazine monohydrate (0.50 mL) in MeOH (5 mL) and $CHCl_3$ (5 mL) was stirred at 60 °C for 25 h and then concentrated. The crude product was recrystallized from MeOH and $CHCl_3$ (1:1) to

give **10** as a white solid (0.26 g, 65%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.75 (br, 1H), 8.22 (s, 1H), 7.59 (br, 1H), 7.24 (br, 1H), 7.12 (br, 1H), 6.36 (s, 1H), 4.64 (s, 2H), 4.59 (s, 2H), 4.16 (s, 2H), 3.44–3.28 (m, 6H), 1.64–1.24 (m, 44H), 0.97–0.85 (m, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=167.0, 166.9, 165.0, 159.2, 158.8, 133.2, 118.0, 115.1, 98.6, 68.3, 39.8, 39.6, 39.5, 31.9, 31.5, 29.6 (d), 29.34, 26.9, 22.7, 20.2, 14.1, 13.8. MS (ESI): *m*/*z* 718.5 $[M+H]^+$, 740.5 $[M+Na]^+$. HRMS (ESI): Calcd for $C_{40}H_{72}N_5O_6$, 718.5477. Found: 718.5467 $[M+H]^+$.

4.1.8. Compound ***37***. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.58 (s, 2H), 7.26 (s, 1H), 7.12 (s, 2H), 6.74 (s, 1H), 4.55 (s, 4H), 4.14 (d, *J*=4.5 Hz, 4H), 3.37–2.93 (m, 10H), 1.55–1.28 (m, 32H), 0.89–0.85 (m, 12H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=168.0, 167.2, 167.0, 158.5, 135.3, 107.1, 106.2, 67.6, 47.0, 46.4, 40.7, 31.5, 31.4, 28.6, 27.5, 26.6, 26.5, 22.5 (d), 14.0, 13.9. MS (ESI): *m*/*z* 733.6 $[M+H]^+$, 755.7 $[M+Na]^+$. HRMS (MALDI-FT): Calcd for $C_{39}H_{69}N_6O_7$ $[M+H]^+$: 733.5222. Found: 733.5218.

4.1.9. Compound ***2***. To a stirred solution of **11** (27 mg, 0.14 mmol), cooled in an ice-bath, in CH_2Cl_2 (4 mL) were added EDCI (67 mg, 0.35 mmol), HOBt (47 mg, 0.35 mmol), and **9** (0.20 g, 0.28 mmol). The solution was stirred at rt for 6 h, diluted with CH_2Cl_2 (200 mL), and washed with water (100 mL) and brine (100 mL) and dried over sodium sulfate. Upon concentration, the resulting residue was recrystallized in MeOH to give **2** as a white solid (0.15 g, 68%). Mp 261–262 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ=10.48 (s, 2H), 10.46 (s, 2H), 8.62 (br, 2H), 8.44 (br, 2H), 8.32 (br, 2H), 8.07 (s, 2H), 7.72 (d, *J*=7.5 Hz, 2H), 7.34 (t, *J*=7.5, 7.5 Hz, 1H), 6.82 (s, 2H), 4.79 (s, 4H), 4.72 (s, 4H), 4.01 (s, 3H), 3.32–3.11 (m, 12H), 1.54–1.13 (m, 88H), 0.92–0.81 (m, 18H). MS (MALDI-TOF): *m*/*z* 1619.7 $[M+Na]^+$. HRMS (MALDI-TOF): Calcd for $C_{89}H_{147}N_{10}O_{15}$, 1596.1054. Found: 1596.1042 $[M+H]^+$. Anal. Calcd for $C_{89}H_{146}N_{10}O_{15}$: C, 66.97; H, 9.22; N, 8.78. Found: C, 66.53; H, 9.46; N, 8.58%.

4.1.10. Compound ***14***. To a stirred solution of **12** (1.00 g, 5.50 mmol) and **13** (1.40 g, 5.50 mmol) in CH_2Cl_2 (10 mL), cooled in an ice-bath, was added DCC (1.40 g, 6.50 mmol). The mixture was stirred at rt for 48 h and the formed precipitate filtrated off. The filtrate was concentrated and the resulting residue triturated in ether (50 mL). The organic phase was washed with water (20 mL) and brine (20 mL) and dried over sodium sulfate. Upon removal of the solvent, the crude product was purified by column chromatography (AcOEt/PE 1:10) to give **14** as a colorless oil (0.32 g, 14%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.41 (t, *J*=6.6, 6.6 Hz, 2H), 3.29–3.16 (m, 4H), 2.31 (t, *J*=7.2, 7.2 Hz, 2H), 1.93–1.75 (m, 4H), 1.51 (br, 4H), 1.27–1.25 (m, 20H), 0.89–0.83 (m, 6H). MS (ESI): *m*/*z* 426.1 $[M+Na]^+$.

4.1.11. Compound ***15***. A suspension of **7** (0.10 g, 0.37 mmol) and K_2CO_3 (0.35 g, 2.5 mmol) in DMF (3 mL) was stirred for 20 min and then **14** (0.40 g, 1.00 mmol) and KI (50 mg, 0.30 mmol) added. The mixture was heated at 110 °C for 66 h and then cooled to rt. The solid was filtrated off and the filtrate poured into aqueous HCl (1 N, 70 mL). The solution was extracted with CH_2Cl_2 (30 mL×2). The organic phase was washed with saturated sodium $NaHCO_3$ solution (20 mL) and brine (20 mL) and dried over sodium sulfate. Upon removal of the solvent, the crude product was purified by column chromatography (AcOEt/PE 1:1) to give **15** as a yellow oil (0.07 g, 14%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.74 (s, 1H), 7.72 (t, *J*=5.4, 5.4 Hz, 1H), 6.44 (s, 1H), 4.19–4.06 (m, 4H), 3.82 (s, 3H), 3.48–3.42 (m, 2H), 3.31–3.17 (m, 8H), 2.42–2.33 (m, 4H), 1.97–1.77 (m, 8H), 1.62–1.34 (m, 10H), 1.26 (br, 42H), 0.96–0.84 (m, 15H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=172.0, 171.2, 165.2, 164.2, 162.6, 160.8, 137.0, 113.9, 112.8, 96.8, 69.1 (d), 51.5, 47.9 (d), 46.0, 45.9, 39.4, 32.5, 32.1, 31.8, 31.7 (d), 29.3 (d), 29.2 (d), 29.1, 28.8, 28.7, 27.8, 27.1, 26.9, 22.6, 21.9, 21.7, 20.2, 14.0, 13.8. MS (ESI): *m*/*z* 914.8 $[M+H]^+$, 936.7 $[M+Na]^+$. HRMS (ESI): Calcd for $C_{55}H_{99}N_3O_7Na$: 936.7375. Found: 936.7382 $[M+Na]^+$.

4.1.12. Compound ***16***. A solution of **15** (60 mg, 0.07 mmol) and LiOH hydrate (11 mg, 0.24 mmol) in THF (0.5 mL), MeOH (2 mL) and water (1 mL) was stirred at rt for 53 h and then aqueous HCl (1 N) was added to pH=3. The mixture was concentrated and the resulting residue triturated with $CHCl_3$ (10 mL). The organic phase was washed with water (10 mL) and brine (10 mL) and dried over sodium sulfate. The solvent was then removed and the resulting residue subjected to column chromatography (AcOEt/PE) to give **16** as a colorless oil (46 mg, 78%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.92 (s, 1H), 7.59 (t, *J*=5.1, 5.1 Hz, 1H), 6.50 (s, 1H), 4.27–4.17 (m, 4H), 3.48–3.39 (m, 2H), 3.31–3.12 (m, 8H), 2.39 (t, *J*=6.9, 6.9 Hz, 4H), 2.01–1.84 (m, 8H), 1.60–1.36 (m, 10H), 1.27 (br, 42H), 0.96–0.84 (m, 15H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=172.1, 171.5, 167.9, 164.5, 161.1, 137.7, 132.6, 131.1, 129.1, 97.3, 72.0, 70.2, 69.5, 48.2, 48.1, 46.3, 39.7, 32.5, 32.4, 32.0 (d), 31.9, 29.9, 29.6 (d), 29.5, 29.4 (d), 29.3, 29.0, 28.8, 28.1, 28.0, 27.9, 27.3, 27.2, 27.1, 22.8, 21.9, 21.8, 20.5, 19.4, 14.3, 14.1. MS (ESI): *m*/*z* 900.8 $[M+H]^+$, 922.7 $[M+Na]^+$. HRMS (ESI): Calcd for $C_{54}H_{97}N_3O_7Na$: 922.7219. Found: 922.7200 $[M+Na]^+$.

4.1.13. Compound ***22***. ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.52 (s, 1H), 8.27 (s, 1H), 8.07 (s, 1H), 7.96 (s, 1H), 6.42 (s, 1H), 4.79 (s, 2H), 4.57 (s, 2H), 4.19 (s, 4H), 3.41–3.31 (m, 10H), 1.62–1.55 (m, 2H), 1.42–1.09 (m, 14H), 0.95–0.84 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=168.3, 168.1, 167.9, 167.7, 166.3, 164.9, 160.8, 160.4, 136.6, 116.7, 112.1, 98.7, 68.7, 67.8, 41.7, 41.5, 41.1 (d), 41.0, 40.9, 40.1, 31.7, 20.5, 14.2, 14.1, 13.2, 13.1. MS (ESI): *m*/*z* 594.4 $[M+H]^+$, 616.3 $[M+Na]^+$. HRMS (ESI): Calcd for $C_{28}H_{43}N_5O_9Na$ $[M+Na]^+$: 616.2953. Found: 616.2962.

4.1.14. Compound ***27***. ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.52 (t, *J*=4.5 Hz, 1H), 8.32 (s, 1H), 7.96 (t, *J*=4.8 Hz, 1H), 7.84 (t, *J*=5.4 Hz, 1H), 6.47 (s, 1H), 4.79 (s, 2H), 4.62 (s, 2H), 4.20 (s, 2H), 4.19 (s, 2H), 3.48–3.42 (m, 2H), 3.35 (t, *J*=7.8 Hz, 4H), 3.23 (t, *J*=7.8 Hz, 4H), 1.64–1.26 (m, 20H), 0.99–0.89 (m, 15H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=168.4, 168.3, 167.9 (d), 166.3, 164.8, 160.8, 160.3, 136.7, 116.6, 112.2, 98.6, 68.6, 67.7, 47.4, 47.2, 46.6, 46.5, 41.0, 40.9, 40.0, 31.7, 31.0, 30.9, 29.9, 20.5, 20.4 (t), 20.33, 14.1, 14.0 (d). MS (ESI): *m*/*z* 706.4 $[M+H]^+$, 728.4 $[M+Na]^+$. HRMS (ESI): Calcd for $C_{36}H_{59}N_5O_9Na$ $[M+Na]^+$: 728.4205. Found: 728.4193.

4.1.15. Compound ***31***. ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.51 (s, 1H), 8.30 (s, 1H), 7.95–7.92 (m, 2H), 6.45 (s, 1H), 4.79 (s, 2H), 4.61 (s, 2H), 4.19 (d, *J*=4.5 Hz, 4H), 3.48–3.22 (m, 10H), 1.64–1.27 (m, 36H), 0.97–0.85 (m, 15H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=168.1, 168.0, 167.6 (d), 165.9, 164.5, 160.6, 160.1, 136.5, 116.4, 112.0, 98.3, 68.4, 67.5, 47.5, 47.2, 46.7, 46.6, 40.7 (d), 39.8, 31.6, 31.5 (d), 28.7, 27.5 (d), 26.7, 26.6 (d), 26.5, 22.6, 22.5, 20.3, 14.0, 13.9. MS (ESI): *m*/*z* 818.7 $[M+H]^+$, 840.7 $[M+Na]^+$. HRMS (MALDI-FT): Calcd for $C_{44}H_{76}N_5O_9$: 818.5638 $[M+H]^+$. Found: 818.5626.

4.1.16. Compound ***34***. ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.51 (s, 1H), 8.31 (s, 1H), 7.92 (s, 1H), 7.87 (s, 1H), 6.41 (s, 1H), 4.77 (s, 2H), 4.59 (s, 2H), 4.19 (s, 4H), 3.45–3.42 (m, 2H), 3.34–3.18 (m, 8H), 1.61–1.36 (m, 10H), 1.26–1.24 (m, 72H), 0.97–0.87 (m, 15H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=168.0, 167.6, 166.2, 164.6, 160.5, 160.0, 136.5, 116.5, 112.2, 98.3, 68.4, 67.5, 62.2, 47.5, 47.3, 46.7, 46.6, 40.8, 40.7, 39.8, 38.7, 31.9, 31.7, 31.6, 31.5, 29.6, 29.5, 29.4, 29.3, 28.8, 27.6, 27.0, 27.0, 22.7, 22.5, 20.3, 20.0, 14.1, 13.9, 13.7. MS (MALDI-TOF): *m*/*z* 1177.8 $[M+Na]^+$, 1193.9 $[M+K]^+$. HRMS (MALDI-TOF): Calcd for $C_{68}H_{124}N_5O_9$: 1154.9394 $[M+H]^+$. Found: 1154.9398.

4.1.17. Compound ***36***. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.71 (s, 2H), 7.28 (s, 2H), 6.79 (s, 1H), 4.55 (s, 4H), 4.13 (d, *J*=3.6 Hz, 4H), 3.90 (s, 3H), 3.34 (t, *J*=7.8 Hz, 4H), 3.19 (t, *J*=7.8 Hz, 4H), 1.56–1.54 (m, 8H),

1.30–1.29 (m, 24H), 0.89–0.85 (m, 12H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=167.4, 166.7, 166.0, 158.3, 132.6, 109.2, 106.8, 67.4, 52.3, 47.0, 46.3, 40.7, 31.5 (d), 28.7, 27.5, 26.6, 26.5, 22.5 (d), 14.0, 13.9. MS (ESI): *m/z* 733.6 $[M+H]^+$, 755.7 $[M+Na]^+$. Anal. Calcd for $C_{40}H_{68}N_4O_8$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.41; H, 9.25; N, 7.65.

4.1.18. Compound ***18***. A solution of **17** (0.50 g, 2.3 mmol) and hydrazine monohydrate (1.5 mL) in methanol (10 mL) was stirred at 60 °C for 6 h and then concentrated. The crude product was recrystallized from MeOH to give **18** as a white solid (0.26 g, 52%). ^{1}H NMR (300 MHz, DMSO-d_6): δ=9.39 (s, 2H), 7.48 (d, *J*=7.8 Hz, 2H), 7.18 (t, *J*=7.8, 7.8 Hz, 1H), 4.51 (s, 4H), 3.77 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ=165.3, 154.8, 130.8, 129.3, 123.2, 62.3. MS (ESI): *m/z* 225.0 $[M+H]^+$, 246.9 $[M+Na]^+$. Anal. Calcd for $C_9H_{12}N_4O_3$: C, 48.21; H, 5.39; N, 24.99. Found: C, 48.25; H, 5.17; N, 24.95.

4.1.19. Compound ***3***. To a stirred solution of **18** (100 mg, 0.11 mmol), cooled in an ice-bath, in $CHCl_3$ (2 mL) and THF (1 mL) were added EDCI (30 mg, 0.15 mmol), HOBt (20 mg, 0.15 mmol), and **16** (12 mg, 0.05 mmol). The solution was stirred at rt for 26 h and then concentrated. After workup, the resulting residue was subjected to column chromatography (AcOEt/CH_2Cl_2 1:1) to give **3** as a ropy yellow oil (35 mg, 32%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.78 (d, *J*=6.9 Hz, 2H), 10.66 (d, *J*=6.9 Hz, 2H), 9.02 (s, 2H), 8.20 (d, *J*=7.5 Hz, 2H), 7.59 (t, *J*=5.4, 5.4 Hz, 2H), 7.35 (t, *J*=7.8, 7.8 Hz, 1H), 6.52 (s, 2H), 4.29–4.14 (m, 11H), 3.50–3.44 (m, 4H), 3.32–3.18 (m, 16H), 2.50 (t, *J*=6.9, 6.9 Hz, 4H), 2.40 (t, *J*=6.9, 6.9 Hz, 4H), 2.18–1.82 (m, 16H), 1.59–1.36 (m, 20H), 1.25 (br, 84H), 0.96–0.82 (m, 30H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=171.9, 171.2, 164.0, 160.7, 160.1, 159.8, 159.0, 156.7, 137.0, 135.0, 125.33, 125.1, 116.0, 112.1, 96.3, 70.0, 69.4, 64.6, 47.9, 47.9, 46.0 (d), 39.5, 32.4, 32.1, 31.8, 31.7 (d), 29.7, 29.4, 29.3 (d), 29.2, 29.1, 28.8, 28.7, 27.8, 27.1, 26.9, 22.6 (d), 22.0, 21.7, 20.3, 14.1 (d), 13.8. MS (MALDI-TOF): *m/z* 2010.5 $[M+Na]^+$. HRMS (MALDI-TOF): Calcd for $C_{117}H_{202}N_{10}O_{15}Na$ $[M+Na]^+$: 2010.5243. Found: 2010.5225.

4.1.20. Compound ***4a***. ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.34 (s, 4H), 8.44–8.39 (m, 4H), 8.27 (s, 2H), 7.96 (d, *J*=7.5 Hz, 2H), 7.85 (s, 2H), 7.16 (t, *J*=7.2 Hz, 1H), 6.48 (s, 2H), 4.79 (s, 4H), 4.75 (s, 4H), 4.16–4.11 (m, 11H), 3.41–3.22 (m, 20H), 1.63–1.53 (m, 4H), 1.42–1.31 (m, 4H), 1.23–0.89 (m, 30H). ^{13}C NMR (125 MHz, CD_3OD): δ=168.2, 168.1, 167.6, 167.1, 165.0, 164.8, 164.4, 159.0, 157.7, 156.2, 133.4, 133.2, 126.3, 123.4, 116.4, 114.7, 97.9, 67.1, 66.9, 63.0, 40.5, 39.9, 39.7, 38.9, 30.5, 19.3, 12.3, 11.3, 11.2. MS (MALDI-TOF): *m/z* 1397.1 $[M+Na]^+$. HRMS (MALDI-TOF): Calcd for $C_{65}H_{94}N_{14}O_{19}Na$ $[M+Na]^+$: 1397.6712. Found: 1397.6728.

4.1.21. Compound ***4b***. ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.36 (s, 2H), 10.24 (s, 2H), 8.70 (s, 2H), 8.46 (s, 2H), 8.40 (s, 2H), 8.15 (d, *J*=7.8 Hz, 2H), 7.41 (t, *J*=5.4 Hz, 2H), 7.32 (t, *J*=7.8 Hz, 1H), 6.45 (s, 2H), 4.87 (s, 4H), 4.80 (s, 4H), 4.23–4.18 (m, 11H), 3.49–3.43 (m, 4H), 3.37–3.19 (m, 16H), 1.62–1.17 (m, 40H), 0.94–0.83 (m, 30H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=167.9, 167.6, 167.5, 167.4, 164.5, 162.5, 162.2, 159.2, 158.3, 156.8, 135.4, 134.7, 125.6, 124.4, 117.7, 114.2, 97.8, 67.9, 67.7, 64.6, 46.9, 46.0, 40.7, 39.8, 31.5, 30.8, 30.7, 29.7, 29.6, 20.2, 20.1 (d), 13.8, 13.7. MS (MALDI-TOF): *m/z* 1621.5 $[M+Na]^+$, 1638.6 $[M+K]^+$. HRMS (MALDI-TOF): Calcd for $C_{81}H_{126}N_{14}O_{19}Na$ $[M+Na]^+$: 1621.9216. Found: 1621.9239.

4.1.22. Compound ***4c***. ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.35 (s, 4H), 8.59 (s, 2H), 8.45 (s, 2H), 8.30 (s, 2H), 8.07 (d, *J*=7.5 Hz, 2H), 7.58 (t, *J*=5.4 Hz, 2H), 7.25 (t, *J*=7.5 Hz, 1H), 6.45 (s, 2H), 4.84 (s, 4H), 4.78 (s, 4H), 4.21–4.16 (m, 11H), 3.47–3.17 (m, 20H), 1.63–1.20 (m, 72H), 0.95–0.81 (m, 30H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=167.9, 167.5, 164.3, 161.8, 161.7, 159.2, 158.4, 156.8, 135.7, 134.9, 125.6, 124.6, 117.9, 114.2, 97.7, 67.9, 67.7, 64.8, 47.2, 46.4, 40.7, 39.8, 31.6, 31.5 (d), 31.4, 28.7, 27.6, 26.7, 26.6, 26.5, 22.6, 22.5, 20.2, 14.0 (d), 13.8. MS (MALDI-TOF): *m/z* 1845.2 $[M+Na]^+$. HRMS (MALDI-FT): Calcd for $C_{97}H_{159}N_{14}O_{19}$: 1824.1901 $[M+H]^+$. Found: 1824.1903.

4.1.23. Compound ***4d***. ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.34 (s, 4H), 8.64 (s, 2H), 8.45–8.44 (br, 2H), 8.31 (s, 2H), 8.12 (d, *J*=7.5 Hz, 2H), 7.48 (s, 2H), 7.30 (t, *J*=7.5 Hz, 1H), 6.44 (s, 2H), 4.86 (s, 4H), 4.78 (s, 4H), 4.22–4.16 (m, 11H), 3.45 (q, *J*=3.3 Hz, 4H), 3.34–3.14 (m, 16H), 1.59–1.25 (m, 168H), 0.96–0.84 (m, 30H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=167.9, 167.5, 167.3, 164.2, 161.2, 161.1, 159.2, 158.4, 156.9, 136.0, 135.2, 125.6, 124.9, 118.3, 114.2, 97.7, 68.0, 67.7, 65.0, 47.3, 46.5, 40.6, 39.7, 31.9, 31.6, 29.6, 29.5, 29.3, 28.8, 27.6, 27.1, 27.0, 26.9, 22.7, 20.2, 14.1, 13.8. MS (MALDI-TOF): *m/z* 2521.8 $[M+Na]^+$. HRMS (MALDI-TOF): Calcd for $C_{145}H_{254}N_{14}O_{19}Na$ $[M+Na]^+$: 2518.9232. Found: 2518.9259.

4.1.24. Compound ***5***. ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.85 (s, 2H), 10.17–10.16 (br, 2H), 8.02–8.01 (br, 4H), 7.72 (s, 2H), 7.05 (s, 4H), 6.70 (s, 2H), 4.34 (s, 8H), 4.14 (d, *J*=4.5 Hz, 8H), 4.03 (s, 6H), 3.34 (t, *J*=7.5 Hz, 8H), 3.20 (t, *J*=7.5 Hz, 8H), 1.58–1.51 (m, 16H), 1.37–1.21 (m, 48H), 0.91–0.79 (m, 24H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=168.6, 167.6, 162.0, 158.1, 151.3, 135.1, 122.8, 114.6, 107.1, 106.7, 67.1, 56.5, 47.3, 46.4, 40.3, 31.6, 31.4, 28.7, 27.7, 26.6, 22.5 (d), 14.0, 13.9. MS (MALDI-TOF): *m/z* 1677.6 $[M+Na]^+$. HRMS (MALDI-FT): Calcd for $C_{88}H_{142}N_{12}O_{18}Na$ $[M+Na]^+$: 1678.0457. Found: 1678.0483.

4.1.25. Compound ***20***. To a solution of **19** (1.00 g, 7.70 mmol) in $CHCl_3$ (15 mL), cooled in an ice-bath, were added 2-chloroacetic acid (0.73 g, 7.70 mmol), EDCI (1.80 g, 9.30 mmol), and HOBt (0.20 g, 1.50 mmol). The solution was stirred for 41 h then washed with saturated $NaHCO_3$ solution (15 mL), water (15 mL), and brine (15 mL) and dried over sodium sulfate. Upon removal of the solvent, the crude product was purified by column chromatography (AcOEt/PE 5:2) to give **20** as a colorless oil (1.20 g, 75%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.71 (s, 1H), 4.07 (s, 4H), 3.43 (q, *J*=7.2 Hz, 2H), 3.28 (q, *J*=7.2 Hz, 2H), 1.22–1.13 (m, 6H). MS (EI): *m/z* 206 $[M]^+$.

4.1.26. Compound ***32***. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.72 (s, 1H), 4.07 (s, 4H), 3.33 (t, *J*=7.2, 7.2 Hz, 2H), 3.16 (t, *J*=7.8, 7.8 Hz, 1H), 1.55–154 (br, 4H), 1.26 (br, 36H), 0.88 (t, *J*=6.9, 6.9 Hz, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=166.8, 166.2, 47.2, 46.5, 42.6, 41.6, 32.1, 29.8, 29.7, 29.6, 28.9, 27.8, 27.2, 27.1, 22.9, 14.3. MS (ESI): *m/z* 485.4 $[M]^-$. HRMS (ESI): Calcd for $C_{28}H_{56}N_2O_2Cl$ $[M+H]^+$: 487.4025. Found: 487.4013.

4.1.27. Compound ***24***. To a stirred solution of **23** (2.30 g, 13.1 mmol) in CH_2Cl_2 (30 mL), cooled in an ice-bath, were added EDCI (2.5 g, 13.1 mmol), DMAP (0.3 g, 2.4 mmol), and di-*n*-butylamine (2.00 mL, 11.8 mmol). The solution was stirred for 27 h, then washed with saturated $NaHCO_3$ solution (30 mL), water (30 mL), and brine (30 mL) and dried over sodium sulfate. Upon removal of the solvent, the crude product was purified by column chromatography (AcOEt/PE 1:5) to give **24** as colorless oil (2.40 g, 70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.55 (s, 1H), 3.92 (d, *J*=4.5 Hz, 2H), 3.30 (t, *J*=7.5 Hz, 2H), 3.12 (t, *J*=7.5 Hz, 2H), 1.56–1.42 (m, 13H), 1.36–1.21 (m, 4H), 0.94–0.87 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=167.4, 155.6, 79.1, 46.4, 45.6, 41.9, 30.6, 29.5, 28.1, 19.9 (d), 13.6, 13.5. MS (ESI): *m/z* 309.0 $[M+Na]^+$. HRMS (ESI): Calcd for $C_{15}H_{30}N_2O_3Na$ $[M+Na]^+$: 309.2149. Found: 309.2158.

4.1.28. Compound ***29***. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.72 (s, 1H), 4.06 (s, 2H), 4.05 (s, 2H), 3.30 (t, *J*=7.8 Hz, 2H), 3.16 (t, *J*=7.8 Hz, 2H), 1.55–1.53 (m, 4H), 1.29 (br, 12H), 0.91–0.85 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=166.8, 166.2, 47.1, 46.4, 42.6, 41.6, 31.7 (d), 28.8, 27.7, 26.8, 26.7, 22.7 (d), 14.2, 14.1. MS (ESI): *m/z* 319.2 $[M+H]^+$, 341.2 $[M+Na]^+$. HRMS (ESI): Calcd for $C_{16}H_{32}N_2O_2Cl$ $[M+H]^+$: 319.2147. Found: 319.2162.

4.1.29. Compound ***25***. To a stirred solution of **24** (1.74 g, 6.10 mmol) in CH_2Cl_2 (10 mL) was added TFA (4 mL) slowly. The solution was

stirred for 2 h and then concentrated. The resulting residue was dissolved in AcOEt (20 mL) and the solution washed with saturated $NaHCO_3$ solution (20 mL), water (20 mL), and brine (20 mL) and dried over sodium sulfate. The solvent was removed and the obtained oil (0.67 g, 3.60 mmol) dissolved in CH_2Cl_2 (10 mL). To this solution, cooled in an ice-bath, were added 2-chloroacetic acid (0.38 g, 4.00 mmol), EDCI (0.77 g, 4.00 mmol), and DMAP (0.10 g, 0.8 mmol). The solution was stirred for 35 h and then concentrated. After workup, the crude product was subjected to column chromatography (AcOEt/PE 1:3) to give **25** as a colorless oil (0.53 g, 56%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.73 (s, 1H), 4.07 (s, 2H), 4.06 (s, 2H), 3.35 (t, J=7.5, 7.5 Hz, 2H), 3.17 (t, J=8.1, 8.1 Hz, 2H), 1.57–1.48 (m, 4H), 1.36–1.25 (m, 4H), 0.97–0.90 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=166.6, 166.0, 46.7, 46.0, 42.4, 41.4, 30.8, 29.7, 20.2, 20.1, 13.8 (d). MS (ESI): m/z 263.0 $[M+H]^+$, 285.0 $[M+Na]^+$. HRMS (ESI): Calcd for $C_{12}H_{24}ClN_2O_2$ $[M+H]^+$: 263.1521. Found: 263.1521.

Acknowledgements

We thank the National Science Foundation of China (Nos. 20732007, 20621062, 20672137, and 20872167), the National Basic Research Program (2007CB808001), and Chinese Academy of Sciences for financial support.

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