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Hydrogen-bonded benzylidenebenzohydrazide macrocycles and oligomers: testing the robust capacity of an amide chain in promoting the formation of vesicles

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ABSTRACT

This Letter describes 2-(2-(dioctylamino)-2-oxoethyl-amino)-2-oxoethoxyl (DOAOE)-tuned self-assembly of vesicles from rigid macrocycles and foldamer-like oligomers. The molecules are prepared through the formation of reversible hydrazone bonds from aldehyde and benzo-hydrazide precursors, which are further facilitated by intramolecular N···H–O hydrogen bonding. SEM, AFM, and fluorescent encapsulation studies reveal that the molecules all self-assemble into vesicular structures in methanol, while similar molecules bearing the triethylene glycol or *n*-decyl chains do not. The results illustrate that DOAOE is robust in promoting the formation of vesicles for aromatic systems in polar solvents.

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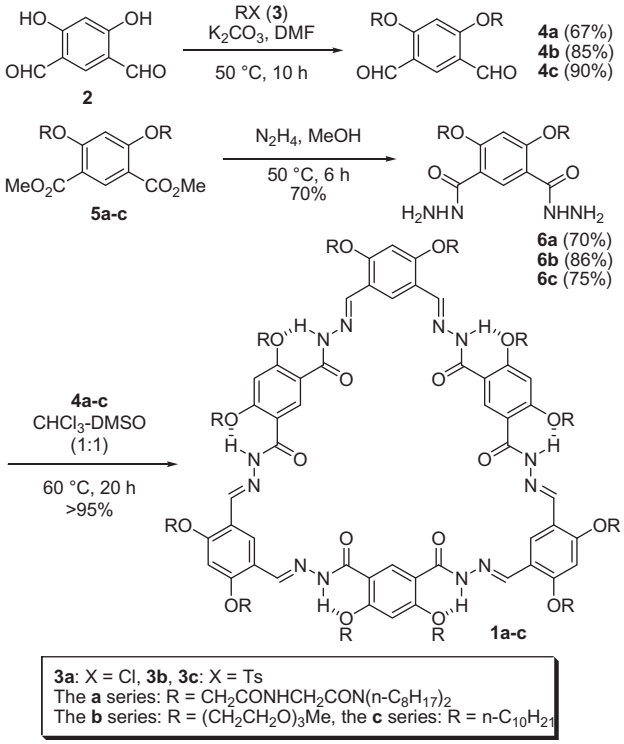
The self-assembly of aromatic systems into vesicular architectures is controlled not only by the backbones themselves, but also by their appended flexible chains.[1] For example, the formation of vesicles by *m*-phenylene ethynylene-based macrocycle, oligo(*p*-phenylenevinylene), or sexithiophene derivatives in polar media is tuned by their amphiphilic triethylene glycol chains,[2–4] while the generation of vesicles by oligo(*p*-phenyleneethynylene) in decane is modulated by the appended dodecyl groups.[5] We recently reported that hydrogen bonding-induced aromatic hydrazide foldamers are capable of forming vesicular architectures in methanol or its aqueous solution.[6] Instead of using the hydrophilic oligoglycol groups that have been widely employed to balance the amphiphilicity of many rigid aromatic segments,[2–4] we developed a new aliphatic amide chain, that is, 2-(2-(dioctylamino)-2-oxoethyl-amino)-2-oxoethoxyl unit (DOAOE),[7] to facilitate the formation of the new three-dimensional entities. Previously, we found that this family of chains that are attached with two *n*-octyl units at the end possesses the maximum capacity of inducing vesicles in polar organic solvents.[7] To further test if DOAOE works for other kinds of aromatic backbones, we have synthesized new DOAOE-bearing macrocyclic and linear molecules through the multicomponent formation of the hydrazone bonds from simple aldehyde and benzo-hydrazide precursors. This dynamic covalent approach has been chosen because it enabled a quick access to molecules of different shapes or conformations and thus remarkably simplified the synthesis of the investigated molecules.



Scheme 1. The synthesis of macrocycles **1a–c**.

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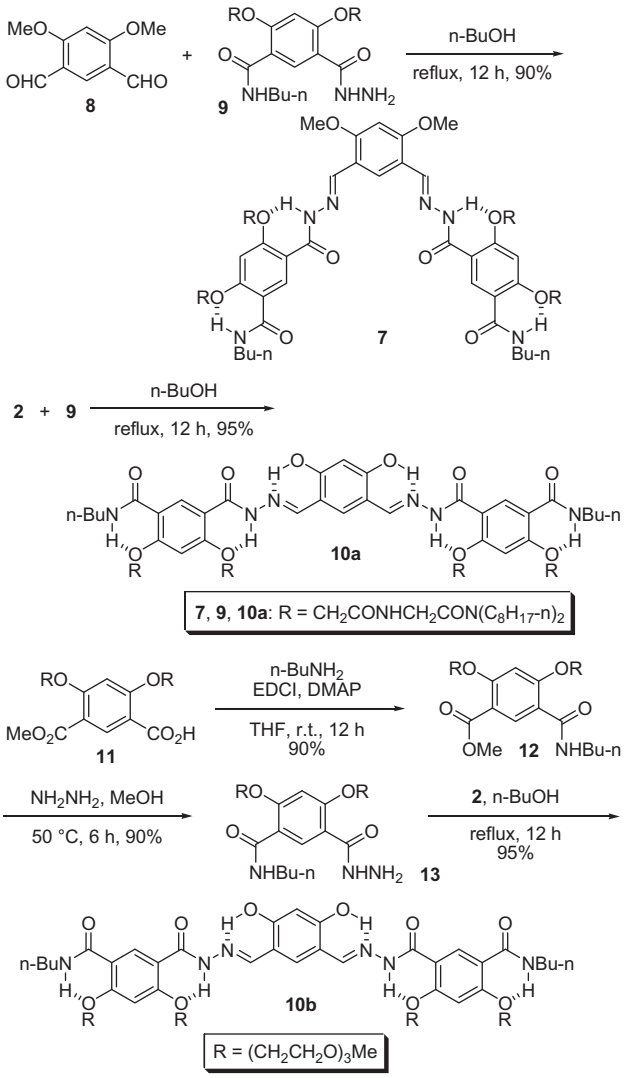
Furthermore, the intramolecular N···H–O hydrogen bonding has been used to facilitate the synthesis and to induce the linear molecules to adopt different conformations. Scanning electron (SEM), atom force (AFM), and fluorescent microscope studies revealed that both new kinds of molecules formed vesicles in methanol. The results are described in this Letter.

To get deep insight into the feature of DOAEO in inducing the formation of vesicular structures, we prepared three macrocyclic and six linear molecules. Macrocycles **1a–c** were prepared according to the routes shown in Scheme 1. Compounds **1b** and **1c** were prepared for the sake of comparison. Thus, isophthalaldehydes **4a–c** were first obtained from the alkylation of **2**[8] in the presence of potassium carbonate in hot DMF. Then, diester **5a-c**[9,10] were treated with an excess amount of hydrazine in hot methanol to give intermediates **6a–c**. Finally, macrocycles **1a–c** were obtained from the reactions of **6a–c** with **4a–c** in the mixture of chloroform and DMSO in nearly quantitative yields.[11] We and others have previously used the similar 3+3 strategy to prepare imine-based macrocycles.[12] This dynamic covalent approach[13] was facilitated by the intramolecular hydrogen bonding[14] as well as the two alkyl groups, through the steric hindrance,[15] in **4a–c**, which forced the resulting hydrazone bonds to adopt the conformation shown in Scheme 1. The ^{1}H NMR tracking experiments in $CDCl_3$/DMSO-d_6 (1:1 v/v) showed that the solutions gave rise to complicated spectra at early stage, which gradually became simpler and finally exhibited only one set of signals. These signals could be assigned to those of the macrocycles by comparing with those of the spectra of the pure samples, reflecting the DCC feature of the reactions.

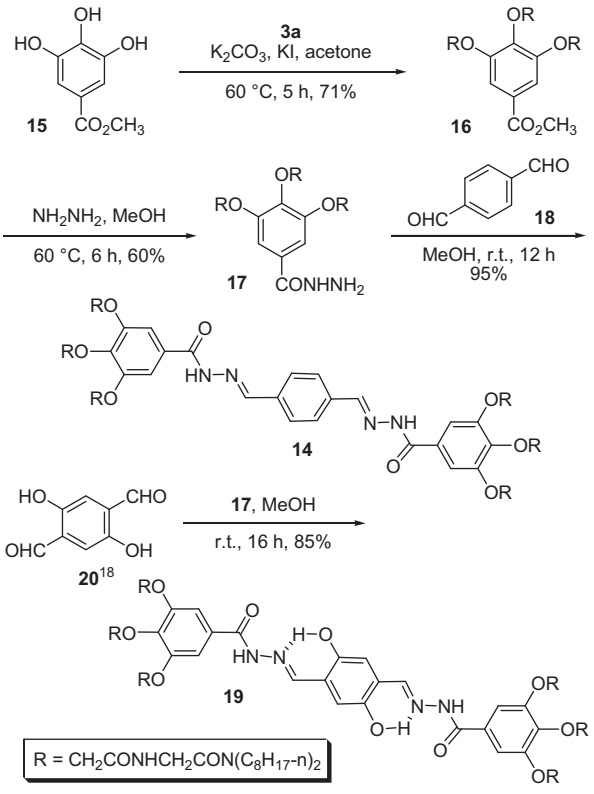
Trimer **7** was prepared from **8**[8] and **9** (1:2 molar ratio),[7a] while **10a** was obtained from the reaction of **2** and **9** (1:2 molar ratio) (Scheme 2). For the preparation of **10b**, analogue of **10a**, **11**[10] was first coupled with *n*-butylamine to afford **12**, which was further treated with hydrazine to produce **13**. The latter was then reacted with **2** (0.5 molar amount) to give **10b** in 95% yield. Due to the electrostatic repulsion between the ether oxygen and imine nitrogen,[15] **7** was expected to have a crescent conformation, while **10a** and **10b** should have an extended conformation owing to the two intramolecular hydrogen bonds of the hydroxyl groups.[16] By using the similar procedures,[17] straight trimers **14** and **19**, whose ends were attached with six DOAOE groups, were also prepared, as shown in Scheme 3.

Although the hydrazone bonds are theoretically reversible, ^{1}H NMR spectra showed that all the molecules were stable in polar DMSO-d_6 or CD_3OD (3 mM). The ^{1}H NMR of macrocycles **1a–c** in $CDCl_3$ (in 99.5% purity) gradually gave rise to new small signals after one week, implying that other linear products were formed, presumably due to the existence of water in the solvent. When the solvent was treated with aluminum oxide, no such peaks were observed, implying that trace hydrochloric acid in the solvent could slowly catalyze their isomerization. The stacking of the aromatic backbones should be responsible for the increased stability of these macrocycles in polar solvents. An evidence for this came from the observation that the signals of the aromatic segments in ^{1}H NMR shifted upfield notably (0.07 ppm) in DMSO-*d* when the concentration was increased from 0.25 mM to 5 mM.

SEM was then used to investigate the self-assembling behavior of the samples. The images of all the DOAOE-attached macrocycle and linear trimers showed the formation of vesicular structures for their samples obtained by evaporating the methanol solutions



Scheme 2. The synthesis of trimers **7**, **10a**, and **10b**.



Scheme 3. The synthesis of trimers **14** and **19**.

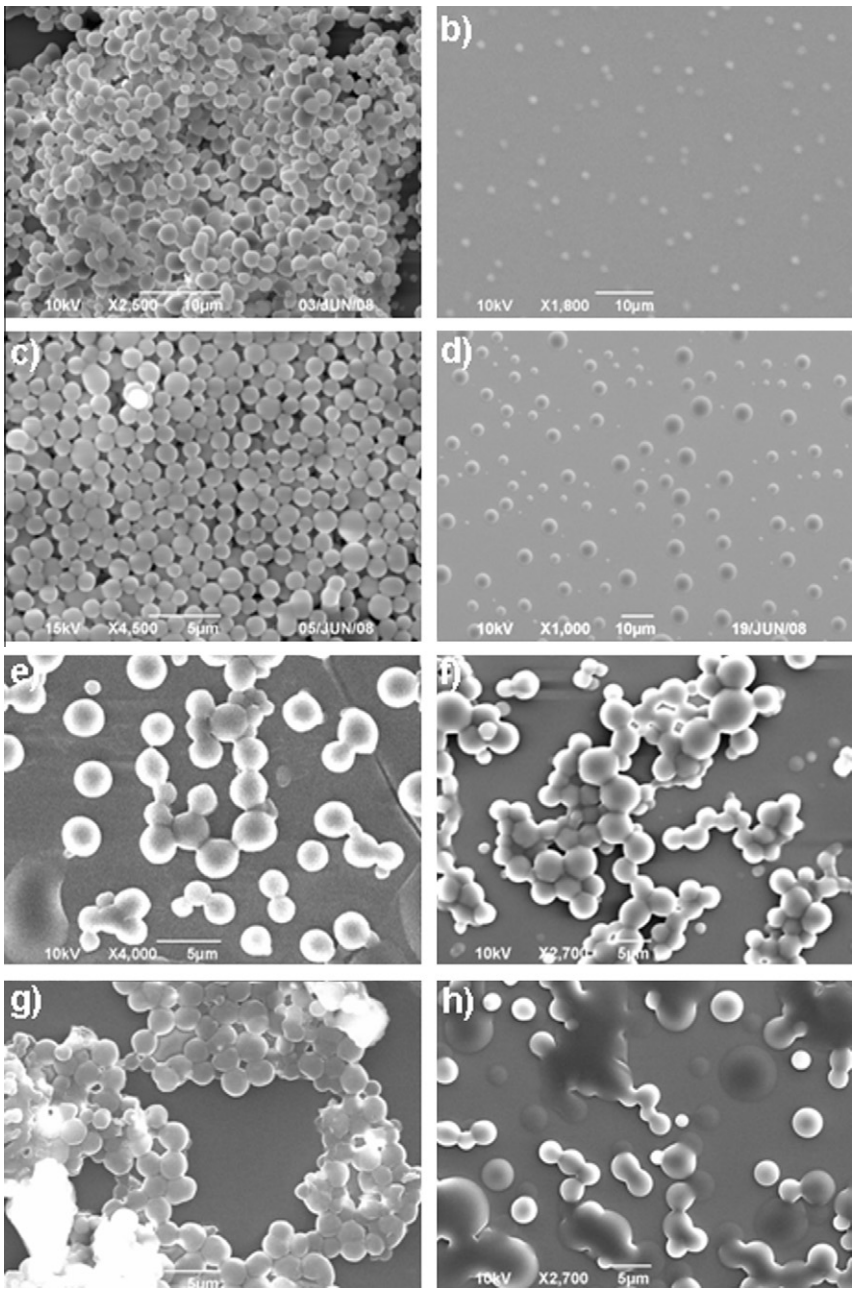
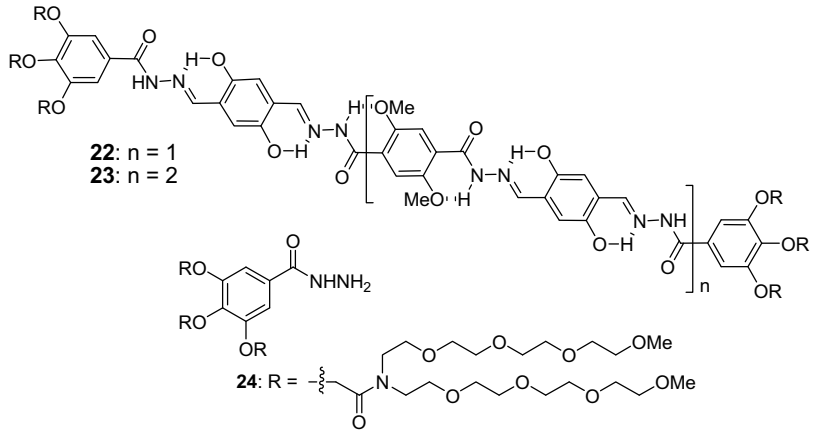


Figure 1. SEM images on mica of (a) **1a**, (b) **1b**, (c) **7**, (d) **10a**, (e) **14**, (f) **19**, (g) **22**, and (h) the mixture of **17**, **20**, and **21** (2:3:2). The samples were obtained from their methanol solution (1 mg/mL) upon evaporation of the solvent. For **1b**, a 1:1 solution of methanol and water was used.

(Fig. 1). In contrast, macrocycle **1b** did not form similar structures in methanol. The image obtained from the solution of **1b** in the mixture of methanol and water (1:1 v/v) showed the formation of smaller vesicles of lower density (Fig. 1b). We might propose that the increase of the polarity of the medium enhanced the stacking tendency of its aromatic backbone and thus promoted it to form the ordered structures.[2] SEM also revealed that macrocycle **1c** did not form vesicles in methanol or its mixture with water, chloroform, or *n*-hexane.

The SEM images of trimers **7**, **10a**, **14**, and **19** are also provided in Figure 1. Their average diameters, obtained by measuring 50 vesicles in a randomly selective square area, are 1.3, 4.5, 5.0, and 4.8 μm, respectively. The value of linear **10a**, **14**, and **19** is notably larger than that of **7** and also **1a** (1.7 μm), implying that the stacking of their aromatic backbone was of higher order. Under the same measurement conditions, SEM of **10b** did not exhibit any vesicular structures. Similar trimers, prepared from the reactions of compound **13** with **8**, 2,3-, or 2,5-dihydroxy- terephthalaldehyde (**20**), did not either. All these observations supported that DOAEO as a side chain is much more robust than the glycol oligomer in inducing the formation of vesicles by aromatic systems in methanol.

To further expand the scope of target molecules, we also performed the reactions of compounds **17**, **20**, and 2,5-dimethoxyterephthalohydrazide (**21**)[7b] in methanol under similar conditions. Their molar ratios were controlled to be 2:2:1 and 2:3:2, respectively. For both reactions, ^{1}H NMR spectra of the crude products in $CDCl_3$ showed that all the starting materials were consumed. MALDI-TOF mass spectrometry exhibited the peaks of **19** at 2552 $[M+Na]^+$, pentamer **22** at 2936 $[M+Na]^+$, and heptamer **23** at



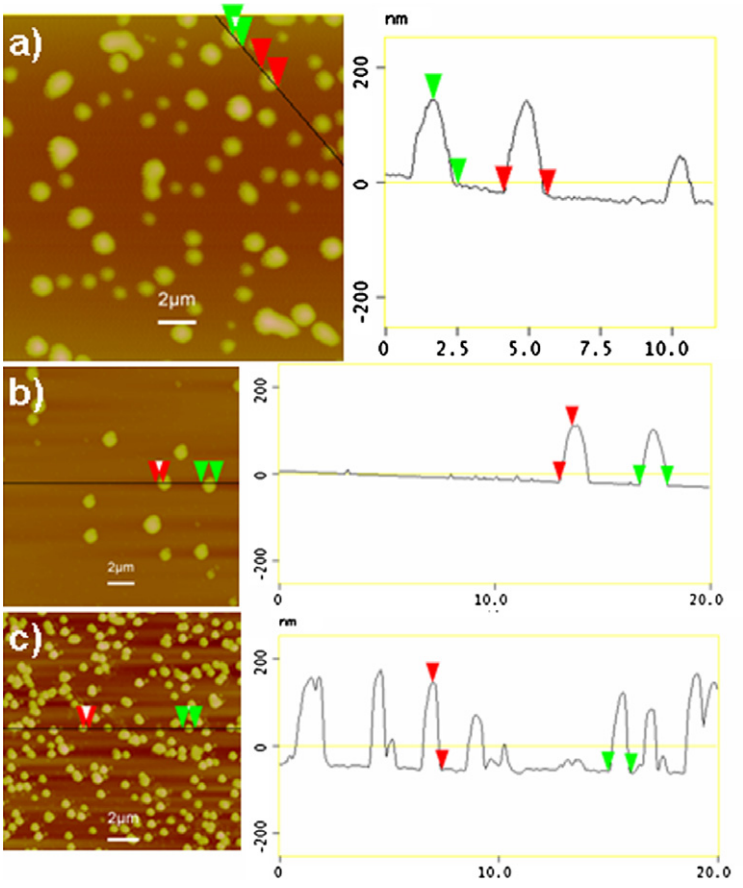


Figure 2. AFM images (the width is 20 μm) on mica of (a) **14**, (b) **19**, and (c) **22**. The samples were obtained from their methanol solution (0.1 mg/mL) upon evaporation of the solvent.

3221 $[M+Na]^+$. Pentamer **22** could be separated in 10% yield from the mixture of the first reaction.[19] Although the reactions gave rise to oligomers of different lengths, SEM images showed that both the mixtures and pure **22** could form vesicles in methanol (Fig. 1g and h). In contrast, the mixtures prepared from the reaction of **24**[20] with **20** and **21** did not generate vesicular structures. Compound **24** was prepared from the corresponding ester[21] and excessive hydrazine in hot methanol. The result again demonstrated the versatility of DOAEO in inducing the formation of vesicles.

AFM also supported the formation of the vesicles in methanol. As examples, the images obtained for **14**, **19**, and **22** are shown in Figure 2. The ratios of the diameter and height of their vesicles were estimated to be about 10, 10, and 5, respectively, indicating important flattening upon being transferred from solution to mica surface, which reflected the evaporation of solvent molecules from the hollow spheres.

Dye-encapsulation experiments were also performed in methanol for compounds **14**, **19,** and **22** (Fig. 3). In the presence of rhodamine B, the vesicles could entrap the dye. After dialysis for 5 days,[7a] the dye in the solution was removed, while the entrapped dye could be kept in the cavity of the vesicles. This result again supported their hollowness and also showed that the membranes of the vesicles were quite stable.

In conclusion, we have described the 2-(2-(dioctylamino)-2-oxoethyl-amino)-2-oxoethoxy (DOAEO)-modulated self-assembly of vesicles by both macrocyclic and linear hydrazone-based aromatic systems in methanol. The linear oligomers have different conformations and their DOAEO chains have been appended at dif-

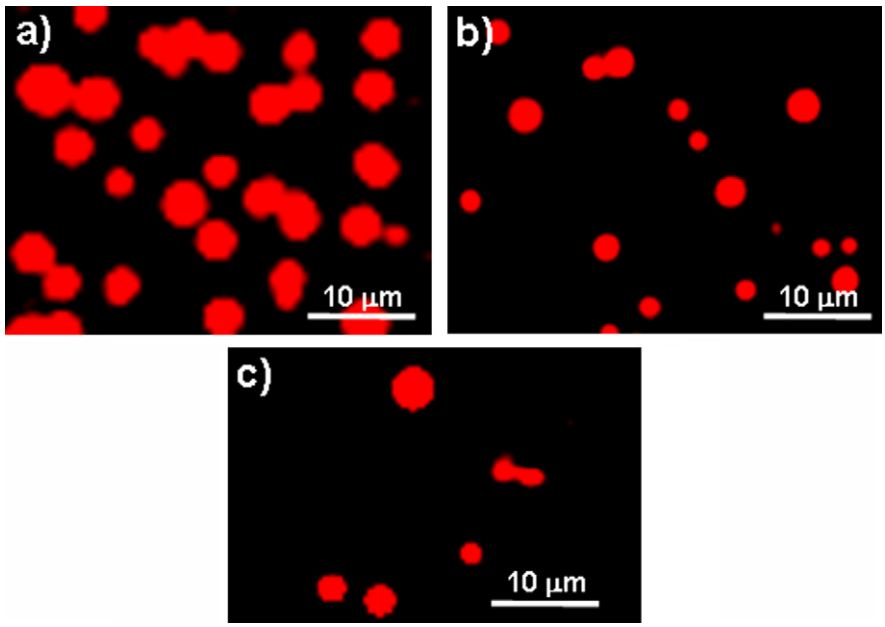


Figure 3. Fluorescence micrographs of vesicles of (a) **14**, (b) **19**, and (c) **22**, formed in methanol (1 mg/mL) in the presence of rhodamine B (1%) after being purified by dialysis for 5 days.

ferent positions. Therefore, their stacking patterns may be different—to form membranes of mono- or multi-layered structures. However, the results, together with our previous studies, well demonstrate that DOAEO is a new, unique, and useful amphiphilic amide-alkane-hybridized chain for the formation of vesicular structures in polar organic solvents. Because DOAEO can modulate the self-assembly of aromatic backbones of varying shape, in the future we will design new large electron-rich and deficient conjugated disc or linear backbones to assemble vesicular structures, which are expected to exhibit new interesting electron or energy transfer properties within their membranes.

Acknowledgments

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11. *Typical procedure*: A solution of compounds **4b** (92 mg, 0.20 mmol) and **6b** (0.10 g, 0.20 mmol) in the mixture of chloroform (5 mL) and DMSO (5 mL) was stirred at 60 °C for 12 h and then concentrated with a rotavapor. The obtained slurry was dissolved in chloroform (10 mL). The solution was washed with water (5 mL × 2) and brine (5 mL) and dried over sodium sulfate. Upon removal of the solvent, the crude product was recrystallized from ether and petroleum ether to give macrocycle **1b** as a yellow solid (0.18 g, 95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 11.10 (s, 6H), 9.07 (s, 6H), 9.02 (s, 6H), 8.21 (s, 6H), 6.68 (s, 6H), 6.39 (s, 6H), 4.17–3.23 (m, 180H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.7, 160.5, 159.5, 140.8, 137.6, 125.7, 116.5, 113.9, 97.8, 96.5, 71.8, 70.6, 70.4, 70.3 (d), 69.8, 69.4, 68.5, 68.0, 58.9, 58.8. MS (MALDI-TOF): *m/z* 2845.2 $[M+Na]^+$. HRMS (MALDI-TOF): calcd for $C_{132}H_{204}N_{12}O_{54}Na$: 2844.3475. Found: 2844.34782.
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17. *Typical procedure*: A solution of compounds **17** (0.16 g, 0.12 mmol) and **20**[18] (11 mg, 0.06 mmol) in methanol (8 mL) was stirred at room temperature for 16 h and then concentrated with a rotavapor. The resulting residue was recrystallized from methanol to give compound **19a** as a yellow solid (0.13 g, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 11.43 (s, 2H), 10.92 (s, 2H), 8.51(s, 2H), 8.41(s, 2H), 7.40 (d, *J* = 12 Hz, 4H), 6.80 (s, 2H), 4.81 (s, 4H), 4.75 (s, 8H), 4.15 (s, 12H), 3.31 (s, 12H), 3.19 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): 169.6, 168.5, 167.4, 162.3, 151.0, 150.7, 149.7, 140.8, 128.6, 120.3, 117.8, 108.2, 72.9, 68.9, 47.4, 46.6, 41.2, 41.0, 32.0, 29.6, 29.5, 29.0 (d), 27.8, 27.2, 22.8, 14.3. MS (MALDI-TOF): 2584.8 $[M+K+H_2O]^+$. HRMS (MALDI-TOF): calcd for $C_{142}H_{246}N_{16}O_{22}Na$ $[M+Na]^+$: 2550.8514. Found: 2550.8498.
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19. *Compound* **22**: A mixture of compounds **17** (96 mg, 0.08 mmol), **20** (13 mg, 0.08 mmol), and **21** (10 mg, 0.04 mmol) in the mixture of chloroform (6.4 mL) and methanol (1.6 mL) was stirred at room temperature for 48 h and then concentrated. The resulting slurry was subjected to column chromatography (CH_2Cl_2/MeOH 10:1) to give a crude product, which was further recrystallized from petroleum ether and ethyl acetate to give **22** as an orange-yellow solid (10 mg, 10%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 11.26 (t, *J* = 3.6 Hz, 2H), 10.83 (s, 4H), 10.39 (d, *J* = 6.0 Hz, 2H), 8.42 (s, 2H), 8.23 (d, *J* = 1.8 Hz, 2H), 7.84–7.80 (m,

4H), 7.70–7.64 (m, 4H), 7.26 (s, 4H), 6.63 (t, J = 1.2 Hz, 4H), 4.70 (s, 12H), 4.17 (s, 18H), 3.25 (dd, J = 3.3 Hz, 24H), 1.51 (s, 12H), 1.28–1.22 (m, 132H), 0.87–0.81 (m, 36H). MS (MALDI-TOF): m/z 2934.7 $[M+Na]^+$. HRMS (MALDI-TOF): calcd for $C_{160}H_{262}N_{20}O_{28}Na$ $[M+Na]^+$: 2934.9572. Found 2934.9585.

20. Compound **24**. Whitle solid. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.03 (s, 2H), 4.93 (s, 6H), 3.59 (s, 96H), 3.30 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$): 172.4, 168.7, 168.1, 151.6, 128.0, 106.5, 71.8, 71.8, 70.7, 70.4 (t), 70.3, 70.2 (d), 70.0, 69.8, 69.2, 69.0, 68.9, 68.5, 66.8 66.0, 59.8, 58.9, 58.8, 48.1, 47.9, 47.6, 47.1, 46.4, 46.1, 45.8. MS (MALDI-TOF): m/z 1518.2 $[M+Na]^+$. HRMS (MALDI-TOF): calcd for $C_{67}H_{125}N_5O_{31}Na$ $[M+Na]^+$: 1518.8241. Found: 1518.8250.
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