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Self-assembly of vesicles from the stacking of a dipodal F···H–N hydrogen bonded arylamide foldamer

Lu Wang [a], Ze-Yun Xiao [a], Jun-Li Hou [b], Gui-Tao Wang [a], Xi-Kui Jiang [a], Zhan-Ting Li [a,*]

[a] State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, China
[b] Department of Chemistry, Fudan University, Shanghai 200433, China

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ABSTRACT

In this paper, we report the synthesis and self-assembling behavior of an F···H–N hydrogen bonding-induced arylamide-based dipodal foldamer. SEM, AFM, TEM, and XRD studies reveal that this preorganized oligomer stacks to form vesicles in methanol–chloroform (10–70%) binary solvents due to the strong stacking interaction of the folded segments and the supramolecular polymeric feature of the dipodal molecule in the stacked state. In contrast, a simple folded molecule can give rise to vesicles only when the chloroform content is 45–55%.

1. Introduction

Vesicles are unique spherical assemblies with applications in biomimetics, nanomaterials, drug, and gene delivery.[1,2] Inspired by the formation of liposomes from the natural amphiphilic phospholipid in aqueous media driven by the hydrophobic force, chemists have designed an ocean of amphiphilic aliphatic molecules and macromolecules for the assembly of vesicles.[3–6] Another principle for the generation of vesicles concerns the utilization of the solvophobically driven π stacking of rationally designed aromatic monomers. In this context, quite a number of rigid and straight oligo(*p*-phenylene)- and oligo(*p*-phenylene vinylene)-based building blocks have been developed.[7,8] Examples of *ortho*-phenylene ethynylene macrocyclic and linear arylamide monomers have also been reported.[9,10] We herein report a novel approach for the self-assembly of vesicles in methanol–chloroform binary solvents from a dipodal F···H–N hydrogen bonding-driven arylamide foldamer by making the stacking interaction as the driving force.

We previously reported a class of arylamide foldamers, whose rigid crescent conformations are stabilized by the intramolecular F···H–N hydrogen bonding.[11] More recently, we found that this series of folded and related macrocyclic frameworks can stack with fullerenes and coronene more strongly than the (Me)O···H–N hydrogen bonded arylamide counterparts,[12] because the ether methyl groups in the latter system have an important steric hindrance for any intermolecular stacking. Considering that several (Me)O···H–N hydrogen bonding-induced arylamide foldamers have been revealed to assemble into vesicles or organogels in polar organic solvents,[13] we became interested in designing new F···H–N hydrogen bonding-induced foldamers to produce vesicular structures, because the self-stacking of this series of frameworks might be stronger than their (Me)O···H–N hydrogen bonding-induced analogs. To further enhance the stacking interaction, we have prepared a dipodal foldamer monomer. We envisioned that it might form supramolecular polymeric structures in the stacked state in polar media,[14] which would facilitate the formation of extended membranes and thus vesicles. In this paper, we report the detailed results.

2. Results and discussion

Dipodal compound **T1** and simple foldamer **T2** were prepared. The *N*,*N*-dioctylamide units were introduced to provide solubility in organic solvents. A comparison of their self-assembling behaviors would reveal the possible cooperative effect of the two connected foldamer segments of **T1**. The synthetic route for **T1** is

* Corresponding author. Tel.: +86 21 54925122; fax: +86 21 64166128.
E-mail address: ztli@mail.sioc.ac.cn (Z.-T. Li).

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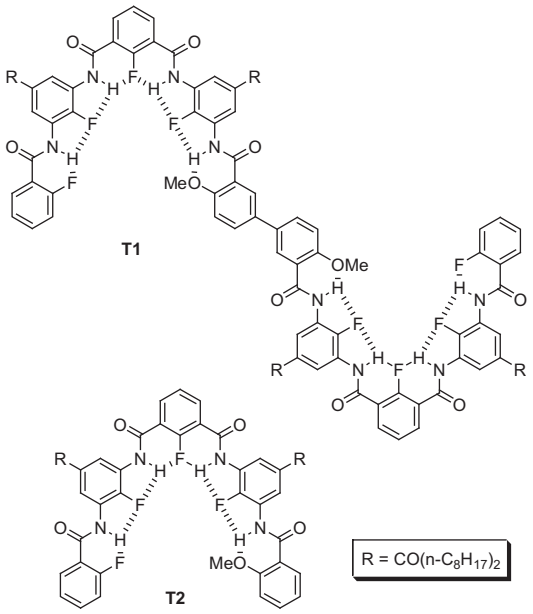
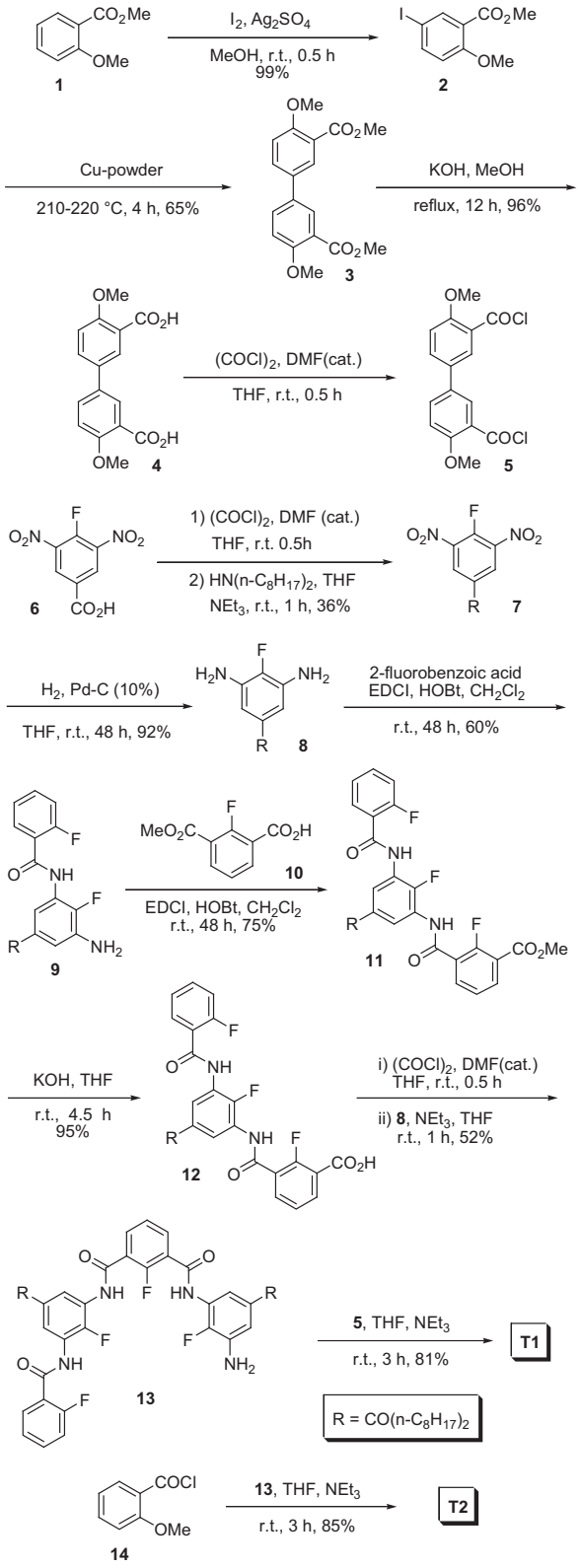
provided in Scheme 1. Thus, ester **1** was first treated with I_2 and Ag_2SO_4 in methanol to give **2** quantitatively. The latter was then self-coupled in the presence of copper powder to give diphenyl **3** in 65% yield. Hydrolysis of **3** with potassium hydroxide in aqueous methanol generated diacid **4**, which was further treated with oxalyl chloride to produce diacyl chloride **5**. With this intermediate available, compound **7** was prepared in 36% yield from **6** and dioctylamine through the acyl chloride as intermediate and then hydrogenated in the presence of Pd–C to give diamine **8** in 92% yield. The latter was coupled with 2-fluorobenzoic acid to give **9** in 60% yield. This aniline was further coupled with **10** to afford ester **11** in 75% yield, which was then hydrolyzed with potassium hydroxide to give acid **12** in 95% yield. The acid was treated with oxalyl chloride to produce the corresponding acyl chloride, which was then coupled with **8** to give amine **13** in 52% yield. Finally, compound **13** was reacted with **5** in THF to afford **T1** in 81% yield, while its reaction with **14** under the similar conditions gave **T2** in 71% yield.



Compounds **T1** and **T2** did not dissolve in methanol, but were soluble in the chloroform–methanol mixture. Their capacity of forming vesicles in this binary solvent system was first investigated by SEM. The representative results are provided in Figure 1. It is found that when the content of chloroform was 10–70%, **T1** formed vesicles in the binary solvents (Fig. 1a–d). Several vesicles showed defects (holes), suggesting that the vesicles were hollow. The images also revealed that, with the increase of the content of chloroform (from 60%), the vesicles began to fuse and when the content was 80%, no vesicular structures could be observed and the images showed only membrane-like structures (Fig. 1e). Compound **T2** also gave rise to vesicles in the binary media, but only when the content of chloroform was in the narrow range of 45–55% (Fig. 1g and h). Below this range, it formed foam-like structures (Fig. 1f) and above the range, like **T1**, it generated membrane-like structures. Both compounds should stack in the binary solvents. However, the greater capacity of **T1** of forming vesicles in the more and less polar solvent systems should reflect its stronger stacking due to its larger aromatic framework. The biphenyl moiety usually has a relatively large torsion angle. Therefore, this greater stacking should be driven by the cooperative interaction of the two arylamide segments due to the F···H–N hydrogen bonding-induced folded conformation. Such intramolecular three-center hydrogen bonding



Scheme 1. The synthetic routes for compounds **T1** and **T2**.

has been revealed to survive in polar media.[13,15] Moreover, in the stacked state, the hydrogen bonding sites should be, to some extent, shielded from the methanol molecules and therefore induced a more rigid folded state.

AFM images also supported **T1** and **T2** formed the vesicles. The result of **T1** is shown in Figure 2. Different from the SEM results, the sizes of the vesicles were generally smaller than the related ones,

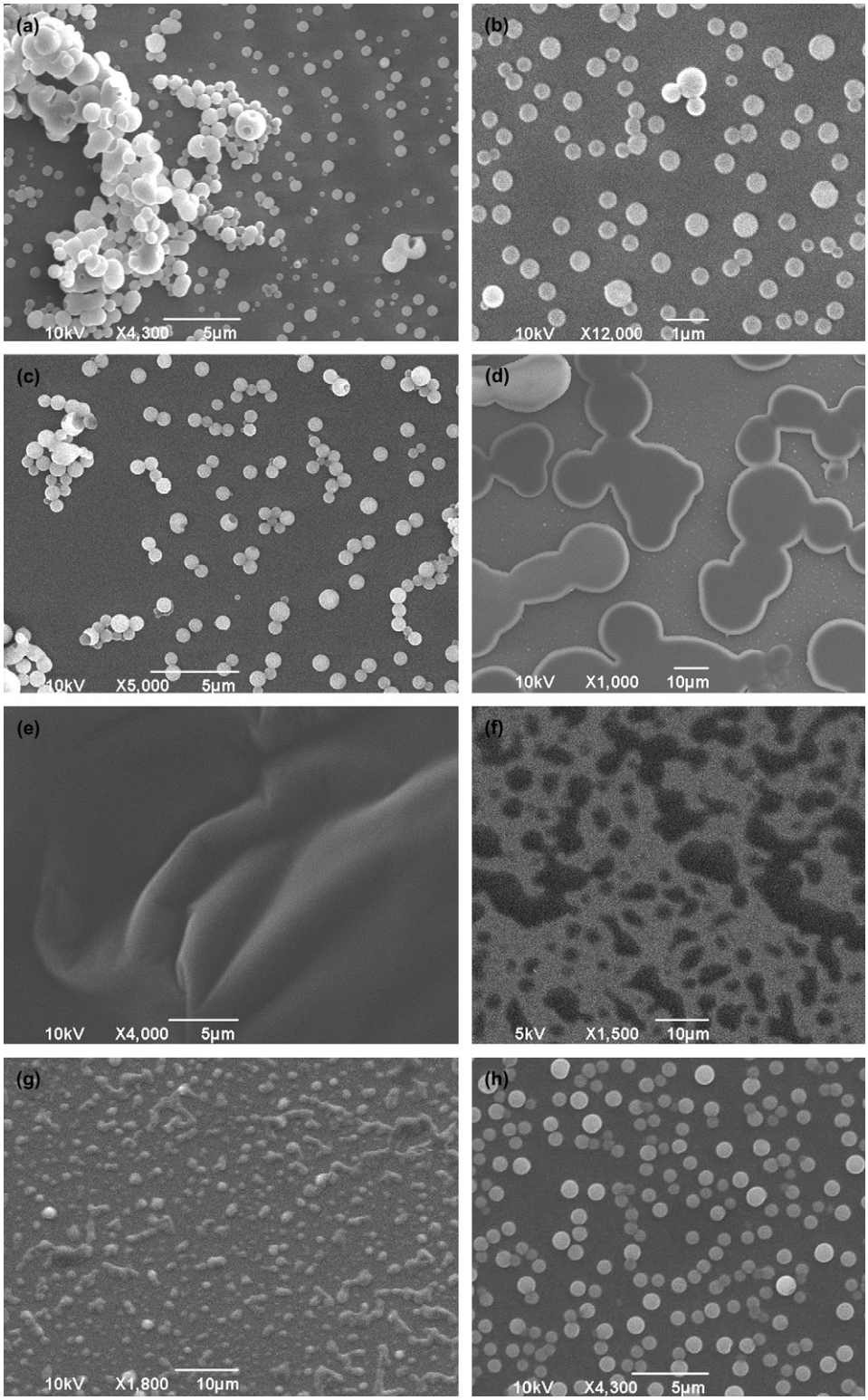


Figure 1. SEM images obtained by evaporation of the solutions (0.4 mM) in the $CHCl_3$/MeOH mixtures of varying ratios on the mica plates. **T1**: a) 10%, b) 30%, c) 50%, d) 70%, and e) 80%; **T2**: f) 10%, g) 30%, h) 50%. The values are the content (v%) of $CHCl_3$ in the binary solvents.

because the image was obtained from a solution of lower concentration for achieving a high resolution. Cross-section analysis of the typical structures revealed that the diameter-height ratios were ca. 16.1 for **T1** and 9.2 for **T2**, which indicated that they were of flattened shape. The results also supported that the spherical structures were hollow and contained solvent molecules,[16] which were evaporated after being transferred from solution to the mica surface.

TEM images further supported the formation of the vesicles by **T1** and **T2** (Fig. 3). The clear contrast between the peripheral and central areas of the spherical aggregates supported their hollow nature, which is typically produced by the projection of the hollow

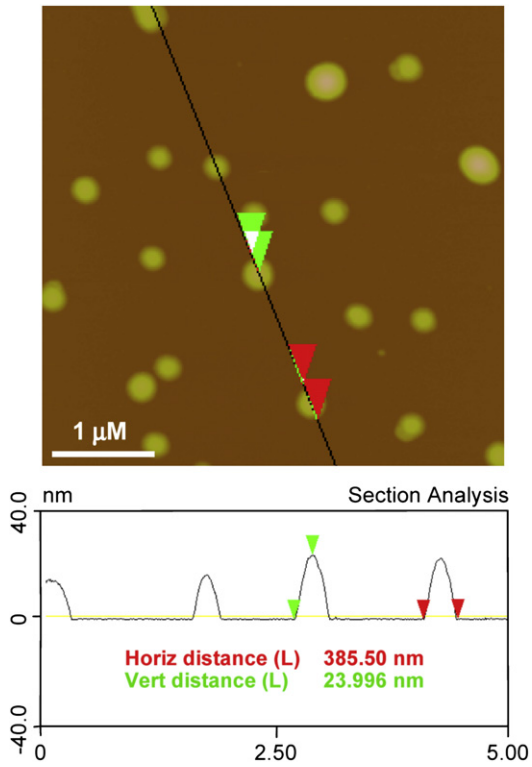


Figure 2. Tapping-mode AFM images (spin-coating) and cross-section analysis of T1, obtained on mica surface by evaporation of the solution (0.01 mM) in $CHCl_3$ and MeOH (1:1).

spheres.[17] High resolution TEM images highlighted that the wall thickness of the vesicular assemblies of both compounds were about 2.8 nm, which was close to the sum of the calculated width (2.6 nm) of their crescent backbones and the length of the extended side chains. Considering that the stacked molecules should exhibit a larger apparent size than that of a single molecule, this result suggested that the vesicles had a monolayer morphology.

The X-ray diffraction (XRD) measurement of the solid sample of **T1**, obtained by evaporating its solution in chloroform–methanol (1:1) revealed a peak at 0.42 nm, which supported a less compact stacking mode (Fig. 4), as observed in other stacked supramolecular aggregates.[18] A similar peak was also observed for **T2**, which was, however, broader and weaker in strength. These results are consistent with the SEM observations, reflecting that the stacking interaction existed for both compounds, but it is stronger for **T1** as a result of the large framework of the dipodal molecule. Both compounds also exhibited a strong peak at 1.51 nm, which is consistent with their calculated size of the folded frameworks (1.52 nm) and thus further supported the monolayer stacking of the molecular in forming the vesicles. The result also indicated that dipodal **T1** mainly stacked along its long 'S'-styled framework rather than the line across the biphenyl moiety (Fig. 5). Molecular dynamic calculation showed that the conformation was more stable than the 'C'-styled conformation. By adopting this stacking pattern, it could form supramolecular polymers to facilitate the formation of the vesicles. The stacking of **T2** was relatively simple and should be similar to that reported for (Me)O···H–N hydrogen bonding-induced arylamide foldamers,[13] although the orientation of the molecules in the column-styled aggregates might be different (Fig. 5).

It has been revealed that the F···H–N hydrogen bonding-induced arylamide foldamers stack strongly with C_{60}.[12a] To get more insight into the assembling mechanism of dipodal **T1**, compound **G1** was also prepared (Scheme 2), the long aliphatic chains of which rendered it soluble in the chloroform–methanol mixture. Fluorescence studies showed that the similar interaction also occurred between it and **T1**, because adding **G1** to the solution of **T1** in chloroform–methanol (1:1) caused a substantial reduction of the emission intensity of **T1**. Job's plot revealed a 1:1 stoichiometry for **G1** and the folded segment of **T1**. On the basis of a nonlinear regression, the apparent association constant for the complex of the folded segment of **T1** and **G1** was estimated to be ca. $2.2\times10^4\ M^{-1}$. SEM images revealed that, adding 1 equiv of **G1** to the solution of **T1** in chloroform–methanol (1:1) completely inhibited the formation of the vesicles by **T1** and the mixture gave rise to fibrous structures. This observation indicated that, the vesicles of **T1** were formed through its ordered stacking, which was weakened in the presence of **G1** due to its strong stacking with **T1**. This latter stacking was less directional due to the global feature of **G1** and therefore only lead to the formation of fibrous structures of less order.

The vesicular aggregates in chloroform and methanol (1:1) were further investigated by the dynamic light scattering (DLS) measurements. The results showed that the vesicles formed by both compounds had a relatively narrow size distribution (Fig. 6), with the intensity-average diameters being 1280 and 615 nm, respectively. The vesicle dimension obtained from the DLS analysis is reasonably in agreement with the SEM studies. The diameter calculated from the DLS analysis is smaller than that observed in the SEM studies (ca. 800 nm), which can be attributed to the vesicles' flattening in the SEM measurements after being transferred from solution to surface.

^{1}H NMR dilution experiments showed no important shifting ($<$0.02 ppm) for the signals in the downfield area, indicating that the folded arylamide structures did not aggregate in pure chloroform. However, reducing the concentration of **T1** in the mixture of chloroform-d and methanol-d_4 (1:1, v/v) from 3.0 mM to 0.3 mM caused the signals of several aromatic protons to shift downfield notably (up to 0.21 ppm). Similar shifting, albeit smaller, was also observed for **T2**. These results further supported that both compounds aggregated through the stacking interaction in the polar media.

3. Conclusions

In this study, we describe a systematic study of the self-assembly of one F···H–N hydrogen bonding-driven dipodal foldamer into vesicular structures. Previous investigations show that the formation of vesicles from (Me)O···H–N hydrogen bonded foldamers is co-driven by the stacking and intermolecular hydrogen bonding in more polar methanol, the present formation of vesicles do not need the involvement of the intermolecular hydrogen bonding due to the enhanced stacking of the folded segments. Because the F···H–N hydrogen bonded foldamers are robust in binding alkyl ammoniums, as the next step, we foresee performing the cross-membrane transportation of the organic cations utilizing the new vesicles. It will be also of interest to prepare tri- or tetrapodal foldamers, which might exhibit new unique supramolecular polymeric features due to the robust stacking of the preorganized segments.

4. Experimental section

4.1. General methods

All reactions were carried out under a dry nitrogen atmosphere. All solvents were dried before use following the standard procedures. Unless otherwise indicated, all starting materials were obtained from commercial suppliers and were used without further purification. Analytical thin-layer chromatography (TLC) was

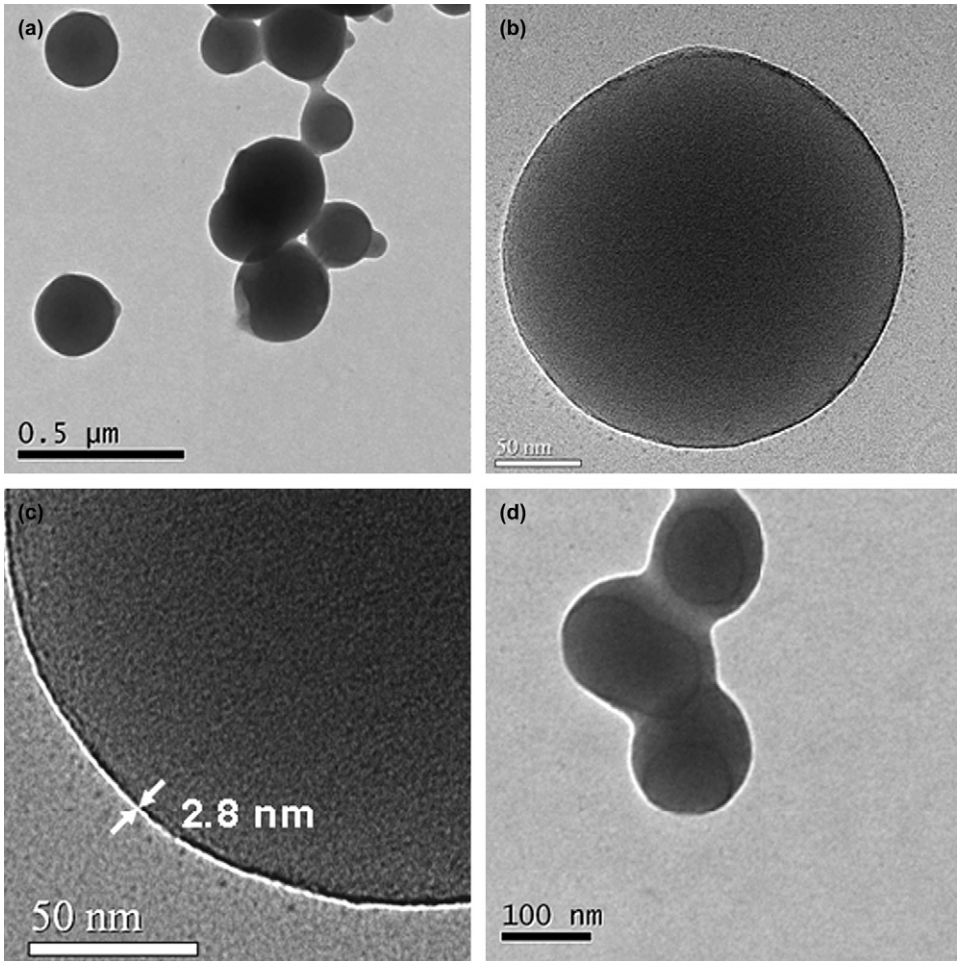


Figure 3. TEM images of **T1** at different scales (a–c) and **T2** (d), obtained from the solutions (0.25 mM) in $CHCl_3$ and MeOH (1:1).

performed on 0.2 mm silica 60 coated on glass plates with F_{254} indicator. The ^1H and ^{13}C NMR spectra were recorded on 300 or 400 MHz spectrometers in the indicated solvents. Chemical shifts are expressed in parts per million (δ) using residual solvent protons as internal standards (^1H: chloroform: δ 7.26 ppm; DMSO: δ 2.49 ppm; ^{13}C: $CDCl_3$: 77.2 ppm). Elemental analysis was carried out at the SIOC analytical center. MALDI MS were obtained on a Voyager-DE STR or IonSpec4.7 Tesla FTMS spectrometer (CHCA or DHB as matrix). SEM images were obtained with a JEOL model JSM-6390LV and the dry samples obtained were shielded with Pt. AFM pictures were obtained in 'tapping' mode on a multimode SPM system equipped with a Nanoscope IV controller. LR-TEM images were recorded on a JEOL JEM-1230 microscope. HR-TEM images were recorded on a JEOL JEM-2010 microscope equipped with energy-dispersive X-ray spectroscopy. The DLS measurement was performed on a Malvern Zetasizer Nano ZS apparatus. XRD experiment was carried out on a Bruker Avance D8 X-ray diffractometer.

4.2. Compound 2

A suspension of compound **1** (2.34 g, 14.1 mmol), iodine (4.06 g, 16.0 mmol) and silver sulfate (5.61 g, 18.0 mmol) in methanol was stirred at rt for 0.5 h and then the solid filtrated off. The filtrate was treated with saturated aqueous sodium sulfite solution until the violet color disappeared and then concentrated under reduced pressure. The resulting residue was extracted with dichloromethane (20 mL) and the organic phase washed with water (20 mL×2) and brine (20 mL), and dried over sodium sulfate. Upon removal of the solvent under reduced pressure, compound **2** was obtained as a white solid (4.07 g, 99%). ^1H NMR (300 MHz, $CDCl_3$): δ 8.07 (d, J=2.3 Hz, 1H), 7.73 (dd, J_1=8.8 Hz, J_2=2.4 Hz, 1H), 6.76 (d, J=8.8 Hz, 1H), 3.88 (s, 6H). MS (EI): m/z 292 $[M]^+$.

4.3. Compound 3

An intimate mixture of compound **2** (1.35 g, 4.62 mmol) and activated copper bronze (3.50 g, 54.6 mmol) was heated under argon at 210–220 °C for 4.5 h and then cooled. The mixture was exhaustively extracted with boiling ethyl acetate (30 mL×2) and the extracts were concentrated with a rotavapor. After workup, the resulting residue was purified by column chromatography (AcOEt/petroleum ether 1:3) to give compound **3** as a white solid (0.47 g, 63%). ^1H NMR (300 MHz, $CDCl_3$): δ 8.00 (d, J=2.4 Hz, 2H), 7.73 (dd, J_1=8.6 Hz, J_2=2.4 Hz, 2H), 6.76 (d, J=8.7 Hz, 2H), 3.94 (s, 6H), 3.92 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.5, 158.3, 131.8, 131.4, 126.7, 120.2, 112.4, 56.1, 52.1. MS (EI): m/z 330 $[M]^+$. Anal. Calcd for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49. Found: C, 65.33; H, 5.59.

4.4. Compound 4

A solution of compound **3** (0.10 g, 0.30 mmol) and potassium hydroxide (0.34 g, 6.07 mmol) in water (7.5 mL) and THF (15 mL) was stirred under reflux for 6 h and then concentrated under reduced pressure. The resulting residue was acidified with hydrochloric acid to pH=1, and then the mixture extracted with ethyl acetate (50 mL×3). The combined organic phase was washed with

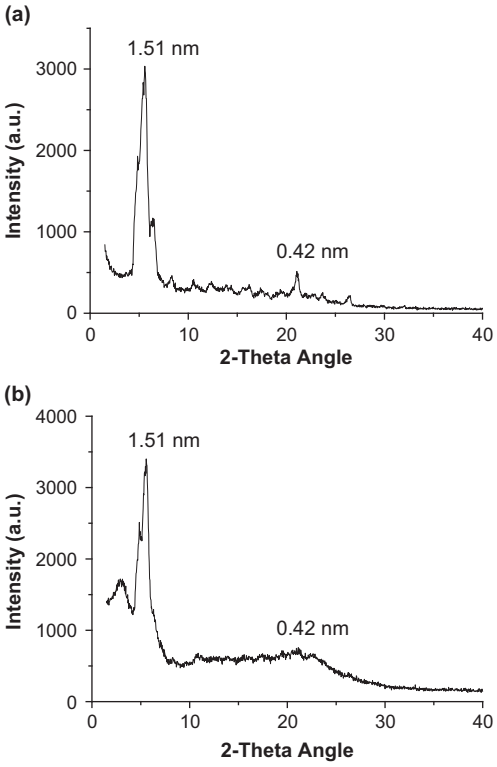


Figure 4. XRD profiles of the aggregates of a) **T1** and b) **T2**. The samples were prepared by evaporating their solutions (0.4 mM) in $CHCl_3$ and MeOH (1:1).

water (50 mL×2) and brine (50 mL), and dried over sodium sulfate. Removal of the solvent under reduced pressure afforded compound **4** as a white solid (0.09 g, 96%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.84 (s, 2H), 7.92–7.85 (m, 4H), 7.27 (s, 2H), 3.95 (s, 6H). MS (EI): m/z 302 $[M]^+$.

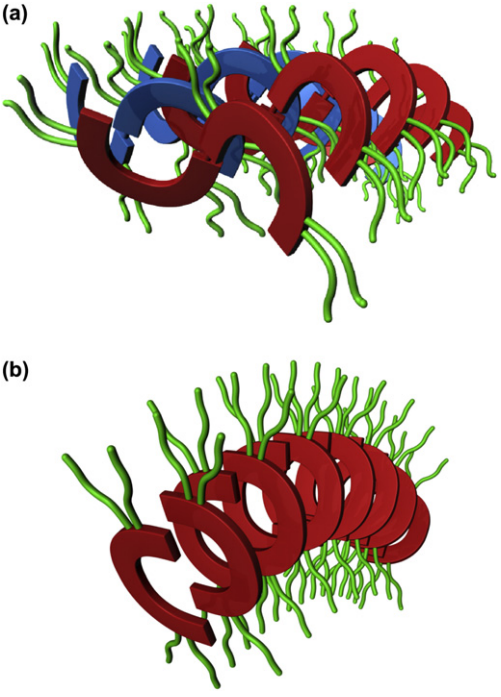
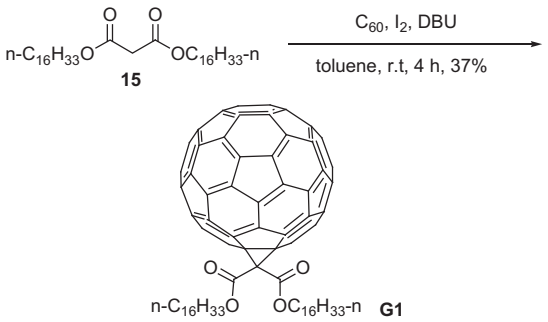


Figure 5. Proposed stacking model of a) **T1** and b) **T2** for the formation of the vesicle walls.



Scheme 2. The synthesis of compound **G1**.

4.5. Compound 7

To a solution of compound **6**[19] (4.00 g, 17.5 mmol) and DMF (0.02 mL) in THF (50 mL), cooled in an ice-bath, was added oxalyl chloride (4.00 mL, 42.1 mmol) dropwise. The mixture was stirred at rt for 0.5 h and then concentrated with a rotavapor. The resulting oily residue was dissolved in THF (20 mL) and the solution was cooled to −10 °C. Then, under stirring, to this solution was added a solution of di-*n*-octyl amine (6.00 mL, 19.8 mmol) and triethylamine (6.00 mL, 43.2 mmol) in THF (20 mL) dropwise. After stirring for another 1 h, the solvent was removed under reduced pressure. The resulting residue was triturated in chloroform (50 mL). The organic solution was washed with water (30 mL×2) and brine (20 mL), and then dried over sodium sulfate. The solvent was removed with a rotavapor, the resulting residue was purified by column chromatography (AcOEt/petroleum ether 1:20) to give compound **7** as a yellow oil (4.20 g, 53%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.33 (d, J=6.0 Hz, 2H), 3.48 (t, J=5.4 Hz, 2H), 3.20 (t, J=5.4 Hz, 2H), 1.29–1.26 (m, 24H), 0.89 (t, J=2.1 Hz, 6H). ^{19}F NMR: δ −123.7 (t, J=6.0 Hz, 1F). This compound was unstable and used for the next step immediately after chromatography.

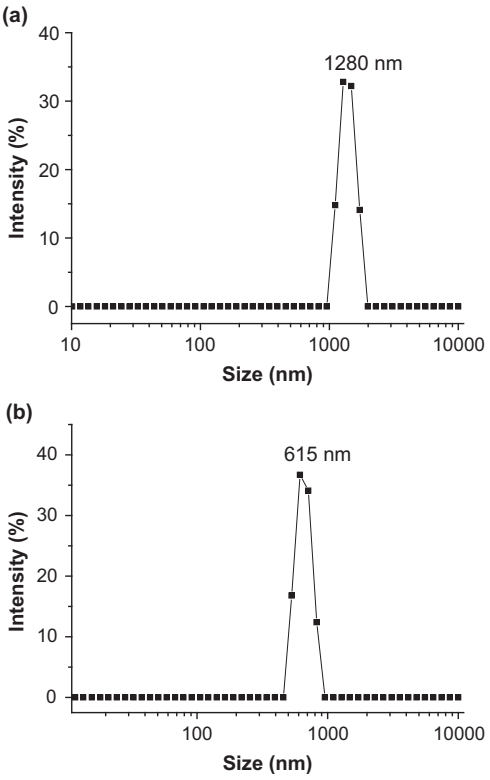


Figure 6. The DLS intensity-weighted distribution of the vesicular aggregates of a) **T1** and b) **T2** in the solution (0.4 mM) of chloroform and methanol (1:1).

4.6. Compound 8

A suspension of compound **7** (1.00 g, 2.20 mmol) and Pd–C (0.1 g) in THF (20 mL) was stirred under hydrogen gas atmosphere (15 psi) at rt for 48 h. The solid was filtered off and the filtrate concentrated under reduced pressure to give compound **8** as a pale yellow solid (0.80 g, 92%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.17 (d, J=7.8 Hz, 2H), 3.72 (s, 4H), 3.43 (t, J=5.4 Hz, 2H), 3.20 (t, J=5.4 Hz, 2H), 1.32–1.29 (m, 24H), 0.89 (t, J=5.4 Hz, 6H). ^{19}F NMR: δ −157.5 (t, J=9.0 Hz, 1F). LR-MS (MALDI-TOF): m/z 394.3 $[M+H]^+$. Anal. Calcd for $C_{23}H_{36}FN_3O$: C, 70.19; H, 10.24; N, 10.68. Found: C, 70.53; H, 10.03; N, 10.32.

4.7. Compound 9

To a stirred solution of compound **8** (0.28 g, 0.71 mmol) and 2-fluorobenzoic acid (0.10 g, 0.71 mmol) in dichloromethane (2.0 mL) were added EDCI (0.15 g, 0.78 mmol) and HOBt (0.11 g, 0.81 mmol). The solution was stirred at rt for 48 h and then diluted with dichloromethane (30 mL). The solution was washed with water (20 mL×2) and brine (20 mL), and dried over sodium sulfate. Upon removal of the solvent under reduced pressure, the resulting residue was purified by column chromatography (AcOEt/CH_2Cl_2 1:10) to give compound **9** as a white solid (0.21 g, 57%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.78 (d, J=8.8 Hz, 1H), 8.18 (t, J=8.2 Hz, 1H), 7.90 (t, J=6.4 Hz, 1H), 7.58–7.51 (m, 1H), 7.35–7.17 (m, 2H), 6.61 (d, J=8.1 Hz, 1H), 3.84 (s, 2H), 3.43 (t, J=7.7 Hz, 2H), 3.25 (t, J=7.7 Hz, 2H), 1.60–1.54 (m, 4H), 1.33–1.08 (m, 20H), 0.88–0.80 (m, 6H). ^{19}F NMR: δ −113.2–113.4 (m, 1F), −152.2 (s, 1F). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 161.6, 160.9, 159.2, 143.2, 140.8, 134.6, 134.5, 134.0, 133.9, 133.6, 133.5, 132.2, 126.2, 125.0 (d), 120.9, 120.8, 116.3, 116.0, 111.1 (d), 109.4, 49.2, 44.9, 31.7, 29.6, 29.3, 29.2, 29.0, 28.6, 27.5, 27.1, 26.6, 22.6, 14.0. MS (EI): m/z 515 $[M]^+$. HRMS (EI): Calcd for $C_{30}H_{44}N_3O_2F_2$ $[M+H]^+$: 516.3403. Found: 516.3396.

4.8. Compound 11

To a solution of compound **10**[20] (0.10 g, 0.51 mmol) and DMF (0.02 mL) in THF (10 mL), cooled in an ice-bath, was added oxalyl chloride (1.00 mL, 10.5 mmol) dropwise. The mixture was stirred at rt for 0.5 h and then concentrated under reduced pressure. The resulting oily residue was dissolved in THF (10 mL) and the solution cooled to −10 °C. Then, under stirring, to this solution was added a solution of compound **9** (0.25 g, 0.48 mmol) and triethylamine (0.5 mL, 3.60 mmol) in THF (10 mL) dropwise. Stirring was continued for another 1 h and the solvent was then removed under reduced pressure. The resulting residue was triturated in chloroform (20 mL). The organic solution was washed with water (10 mL×2) and brine (10 mL), and then dried over sodium sulfate. Upon removal of the solvent in vacuo, the crude product was purified by column chromatography (AcOEt/CH_2Cl_2 1:15) to give compound **11** as a white solid (0.25 g, 75%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.87–8.78 (m, 2H), 8.38–8.31 (m, 2H), 8.26 (d, J=9.0 Hz, 1H), 8.21–8.12 (m, 2H), 7.60–7.53 (m, 1H), 7.53–7.19 (m, 3H), 3.94 (s, 3H), 3.45 (t, J=7.2 Hz, 2H), 3.25 (t, J=7.2 Hz, 2H), 1.62–1.55 (m, 6H), 1.33–1.08 (m, 18H), 0.89–0.77 (m, 6H). ^{19}F NMR: δ −112.6–112.7 (m, 1F), −113.2–113.3 (m, 1F), −145.3 (s, 1F). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.9, 163.9, 161.7, 161.1, 160.7, 160.6, 159.2, 158.1, 144.6, 142.2, 136.6, 136.1, 134.3, 134.2, 133.9, 132.2, 126.3, 126.2, 125.9, 125.1, 124.7, 120.6, 120.5, 116.4, 116.1, 52.7, 49.4, 45.2, 31.8, 31.7, 29.4, 29.2, 29.0, 28.6, 27.5, 27.1, 26.6, 22.6, 22.5, 14.1, 14.0. MS (MALDI-TOF): m/z 718.6 $[M+Na]^+$, 734.5 $[M+K]^+$. HRMS (MALDI-TOF): Calcd for $C_{39}H_{49}N_3O_5F_3$ $[M+H]^+$: 696.3609. Found: 696.3618.

4.9. Compound 12

A solution of compound **11** (0.25 g, 0.36 mmol) and potassium hydroxide (0.19 g, 3.39 mmol) in water (9 mL) and THF (18 mL) was stirred at rt for 4.5 h and then concentrated under reduced pressure. The resulting residue was acidified with hydrochloric acid to pH=1, and then the mixture was extracted with ethyl acetate (15 mL×3), the combined organic phase was washed with water (20 mL×2) and brine (20 mL), and dried over sodium sulfate. Upon removal of the solvent under reduced pressure, compound **12** was obtained as a white solid (0.24 g, 95%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.85–8.71 (m, 2H), 8.40–8.31 (m, 2H), 8.26 (d, J=8.5 Hz, 1H), 8.21–8.12 (m, 2H), 7.60–7.53 (m, 1H), 7.53–7.19 (m, 3H), 3.45 (t, J=7.2 Hz, 2H), 3.25 (t, J=7.2 Hz, 2H), 1.62–1.55 (m, 6H), 1.33–1.08 (m, 18H), 0.89–0.77 (m, 6H). ^{19}F NMR: δ −112.2 (s, 1F), −113.1 (s, 1F), −142.7 (s, 1F). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.0, 165.8, 162.0, 161.5, 161.3, 161.0, 159.5, 158.7, 145.4, 143.0, 136.9, 134.6, 134.5, 133.1, 132.5, 126.6, 126.5, 126.2, 126.1, 125.4, 124.8, 122.2, 122.1, 120.8, 120.6, 120.2, 117.3, 116.6, 116.5, 116.4, 49.9, 45.9, 32.1, 32.0, 29.6, 29.5, 29.3, 28.9, 27.7, 27.4, 26.9, 22.9, 22.8, 14.3, 14.2. MS (ESI): m/z 718.6 $[M+Na]^+$, 734.5 $[M+K]^+$. HRMS (ESI): Calcd for $C_{38}H_{47}N_3O_5F_3$ $[M+H]^+$: 682.3468. Found: 682.3462.

4.10. Compound 13

To a solution of compound **12** (0.25 g, 0.37 mmol) and DMF (0.02 mL) in THF (15 mL), cooled in an ice-bath, was added oxalyl chloride (0.60 mL, 6.31 mmol) dropwise. The mixture was stirred at rt for 0.5 h and then concentrated under reduced pressure. The resulting residue was dissolved in THF (10 mL) and the solution cooled to −10 °C. Then, to this stirred solution was added a solution of compound **8** (0.22 g, 0.56 mmol) and triethylamine (0.5 mL, 3.60 mmol) in THF (10 mL) dropwise. After stirring for another 1 h, the solution was concentrated under reduced pressure. The resulting residue was triturated in chloroform (20 mL). The organic solution was washed with water (10 mL×2) and brine (10 mL), and then dried sodium sulfate. Upon removal of the solvent in vacuo, the crude product was purified by column chromatography (AcOEt/CH_2Cl_2 1:2) to give compound **13** as a white solid (0.20 g, 52%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.05 (d, J=10.88 Hz, 1H), 8.90 (d, J=10.8 Hz, 1H), 8.77 (d, J=12.0 Hz, 1H), 8.30 (d, J=5.5 Hz, 1H), 8.22–8.16 (m, 2H), 8.12–8.06 (m, 2H), 7.80 (d, J=5.5 Hz, 1H) 7.56–7.50 (m, 1H), 7.43 (t, J=7.8 Hz, 1H), 7.31–7.14 (m, 2H), 6.58 (d, J=8.0 Hz, 1H), 3.92 (s, 2H), 3.40–3.37 (m, 4H), 3.24–3.21 (m, 4H), 1.68–1.58 (m, 12H), 1.44–0.96 (m, 36H), 0.89–0.76 (m, 12H). ^{19}F NMR: δ −112.9 (s, 1F), −115.5 (s, 1F), −143.6 (s, 1F), −150.9 (s, 1F). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.8, 170.1, 161.6, 161.5, 161.3, 160.9, 159.1, 159.0, 156.5, 145.2, 143.4, 142.8, 141.1, 134.9, 134.8, 134.1, 134.0, 133.1, 131.9, 126.3, 126.2, 126.0, 125.9, 125.8, 125.7, 124.9, 123.2, 123.0, 122.9, 122.7, 120.6, 120.5, 117.1, 116.3, 116.0, 115.9, 111.1, 109.5, 49.4, 49.2, 45.2, 44.9, 31.8, 31.7, 29.6, 29.3, 29.2, 29.0, 28.9, 28.5, 27.2, 27.1, 26.5, 22.6, 22.5, 14.0, 13.9. MS (MALDI-TOF): m/z 1079.6 $[M+Na]^+$. HRMS (MALDI-TOF): Calcd for $C_{61}H_{85}N_6O_5F_4$ $[M+H]^+$: 1057.6505. Found: 1057.6512.

4.11. Compound T1

To a solution of compound **4** (0.01 g, 0.03 mmol) and DMF (0.02 mL) in THF (4 mL), cooled in an ice-bath, was added oxalyl chloride (0.20 mL, 2.10 mmol) dropwise. The mixture was stirred at rt for 0.5 h and then concentrated under reduced pressure to give compound **5** as a solid. The intermediate was dissolved in THF (2 mL) and the solution was cooled to −10 °C. Then, to this solution under stirring, was added a solution of compound **13** (0.08 g, 0.08 mmol) and triethylamine (0.20 mL, 1.44 mmol) in THF (2 mL) dropwise. Stirring was continued for another 3 h and the solvent

was then removed under reduced pressure. The resulting residue was triturated in chloroform (20 mL). The organic solution was washed with water (10 mL×2) and brine (10 mL), and then dried over sodium sulfate. Upon removal of the solvent in vacuo, the crude product was purified by column chromatography (CH_2Cl_2/MeOH 100:1) to give compound **T1** as a white solid (0.06 g, 81%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.60 (s, 2H), 10.07 (s, 2H), 9.27 (d, J=10.9 Hz, 2H), 8.89 (d, J=19.7 Hz, 2H), 8.44 (d, J=6.4 Hz, 2H), 8.39 (d, J=5.5 Hz, 2H), 8.28–8.23 (m, 6H), 8.14–8.09 (m, 2H), 7.99 (s, 2H), 7.85 (s, 2H), 7.54–7.47 (m, 6H), 7.32–7.31 (m, 2H), 7.13–7.08 (m, 4H), 4.26 (s, 6H), 3.43–3.29 (m, 16H), 1.66–1.64 (s, 16H), 1.34–1.22 (m, 80H), 0.93–0.31 (m, 24H). ^{19}F NMR: δ −112.6 (s, 2F), −116.3 (s, 2F), −144.6 (s, 2F), −144.7 (s, 2F). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 170.1, 162.6, 162.2, 161.6, 161.3, 161.0, 159.2, 157.0, 156.8, 144.7, 144.2, 142.3, 141.8, 134.7, 134.3, 133.7, 132.9, 132.3, 131.3, 130.7, 129.0, 127.3, 126.3, 126.1, 125.2, 124.9, 124.5, 124.3, 122.5, 122.3, 120.7, 120.3, 116.5, 116.2, 115.9, 115.8, 113.6, 111.9, 56.8, 49.5, 45.3, 31.9, 31.7, 29.7, 29.4, 29.2, 29.1, 28.7, 28.5, 27.4, 27.1, 26.5, 22.7, 22.5, 14.1, 13.9. MS (MALDI-TOF): m/z 2380.4 $[M+H]^+$. HRMS (MALDI-FT): Calcd for $C_{138}H_{179}N_{12}O_{14}F_8$: 2380.3531. Found: 2380.3516.

4.12. Compound T2

To a solution of 2-methoxybenzoic acid (15 mg, 0.10 mmol) and DMF (0.02 mL) in THF (10 mL), cooled in an ice-bath, was added oxalyl chloride (0.20 mL, 2.10 mmol) dropwise. The mixture was stirred at rt for 0.5 h and then concentrated under reduced pressure to give compound **14** as a solid. This intermediate was dissolved in THF (5 mL) again and the solution was cooled to −10 °C. Then, to this solution under stirring a solution of compound **13** (50 mg, 0.05 mmol) and triethylamine (0.1 mL, 0.72 mmol) in THF (5 mL) was added dropwise. Stirring was continued for another 3 h and the solvent then removed under reduced pressure. The resulting residue was triturated in chloroform (40 mL). The organic solution was washed with water (20 mL×2) and brine (20 mL) and then dried over sodium sulfate. Upon removal of the solvent in vacuo, the crude product was purified by column chromatography ($CHCl_3$/EtOAc 4:1) to give compound **T2** as a white solid (48 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.42 (d, J=3.2 Hz, 1H), 9.41–9.38 (m, 2H), 8.94 (dd, J_1=2.7 Hz, J_2=16.4 Hz, 1H), 8.42 (dd, J_1=1.8 Hz, J_2=6.7 Hz, 1H), 8.27 (dd, J_1=1.6 Hz, J_2=6.6 Hz, 1H), 8.15–8.08 (m, 4H), 8.04 (dt, J_1=1.8 Hz, J_2=7.9 Hz, 1H), 7.86 (dd, J_1=1.7 Hz, J_2=6.7 Hz, 1H), 7.50–7.44 (m, 1H), 7.40–7.36 (m, 2H), 7.25–7.21 (m, 1H), 7.10 (dd, J_1=8.3, J_2=12.2 Hz, 1H), 7.01–6.97 (m, 1H), 6.86 (d, J=8.3 Hz, 1H), 4.00 (s, 3H), 3.39–3.17 (m, 8H), 1.58–1.53 (m, 8H), 1.30–1.12 (m, 40H), 0.88 (t, J=6.3 Hz, 6H), 0.79–0.73 (m, 6H). ^{19}F NMR: δ −112.6 (s, 1F), −112.3 (s, 1F), −142.7 (s, 1F), −113.1 (s, 1F). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.3, 170.1, 162.9, 161.6, 161.5, 161.4, 161.2, 161.1, 159.1, 157.2, 156.6, 144.9, 142.4, 134.9, 134.7, 134.1, 134.0, 133.5, 133.4, 133.3, 133.2, 133.1, 132.1, 132.0, 127.3, 127.2, 126.4, 126.3, 126.0, 125.9, 125.5, 125.4, 124.9, 124.9, 124.8, 124.8, 123.2, 123.1, 123.0, 122.9, 121.3, 120.6, 120.5, 116.5, 116.2, 116.0, 115.9, 115.8, 115.2, 111.3, 56.1, 49.4, 45.2, 31.8, 31.7, 29.6, 29.3, 29.2, 29.0, 28.9, 28.6, 28.5, 27.4, 27.1, 26.9, 26.5, 22.6, 22.5, 22.5, 14.1, 13.9. LR-MS (MALDI-TOF): m/z 1214.0 $[M+Na]^+$. HRMS (MALDI-FT): Calcd for $C_{69}H_{91}N_6O_7F_4$: 1191.6880. Found: 1191.6900.

4.13. Compound G1

To a stirred solution of C_{60} (72 mg, 0.10 mmol), iodine (66 mg, 0.20 mmol) and compound **15**[21] (55 mg, 0.10 mmol) in toluene (50 mL) was added DBU (34 μL, 0.10 mmol). The solution was stirred at rt for 4 h and then the solvent removed under reduced pressure. The resulting residue was purified by column chromatography (first with CS_2 to remove unreacted C_{60} and then with toluene as eluent) to afford compound **G1** as a dark brown solid (47 mg, 37%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.49 (t, J=6.3 Hz, 4H), 1.84 (t, J=7.2 Hz, 4H), 1.18–1.48 (m, 52H), 0.88 (t, J=6.0 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 163.7, 145.4, 145.3, 145.2, 144.9, 144.7, 144.6, 143.9, 143.1, 143.0, 142.2, 142.0, 141.0, 139.0, 71.8, 67.5, 31.9, 31.4, 30.2, 29.7, 29.6, 29.4, 29.3, 28.6, 26.0, 22.7, 14.1. LR-MS (MALDI-TOF): m/z 1271 $[M+H]^+$. HRMS (MALDI-FT): Calcd for $C_{95}H_{67}O_4$: 1271.5082. Found: 1271.5034.

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