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Synthesis of Hydrophobic Derivatives of the G∧C Base for Rosette Nanotube Self-Assembly in Apolar Media

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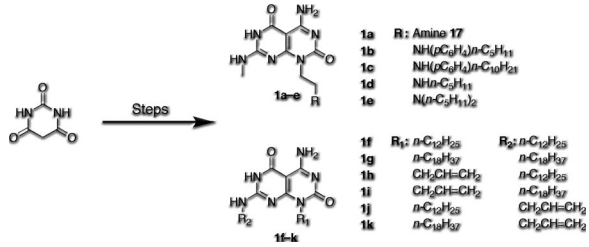

Eleven self-complementary G∧C derivatives bearing hydrophobic moieties were synthesized and characterized. One representative derivative from this family was shown to self-assemble into rosette nanotubes in hexane and form Langmuir−Blodgett films at the air−water interface.

The G∧C motif, a self-cDNA base analogue featuring the hydrogen-bonding arrays of both guanine and cytosine has been shown to self-assemble into rosette nanotubes (RNTs).[1] The first step of this process is the formation of a six-membered supermacrocycle (rosette) maintained by 18 hydrogen bonds, which then stack to form a tubular structure with an inner diameter of 1.1 nm.[1,2] The RNTs are a promising class of materials due to their synthetic accessibility and amenability to chemical functionalization. For instance, RNTs with different surface groups displaying chiroptical[1a] and hierarchical[1b] tunability, high thermal stability,[1b] and entropically driven self-assembly behavior[1c] in aqueous or polar solvents have been reported.

Here we report on the synthesis of 11 G∧C derivatives with hydrophobic substituents. These candidates were targeted to explore potential applications of RNTs as discotic liquid crystals,[3] channels,[4] nanowires,[5] and LB films[6] in nonacqueous (polar and apolar) solvents. We have also shown that a representative G∧C derivative (**1f**) from this family undergoes self-assembly in hexane to form RNTs and Langmuir−Blodgett films at the air−water interface.

Our initial attempt at functionalizing the G∧C motif consisted in coupling alkene **10** to commercially available aryl halides using the Heck reaction.[7] Unfortunately, this reaction did not proceed. Cross-metathesis attempts between alkene **10** and *p*-bromostyrene using Grubbs' second-generation catalyst[8] were equally unsuccessful. Our next strategy consisted of reductively coupling G∧C aldehyde **11** with Percec's dendrons[9] (**13**−**16**, Scheme 1). Unfortunately, preliminary stability tests even under mild acidic conditions required for the final deprotection step led to their decomposition at the benzylic positions. To eliminate this problem we synthesized arylamine derivative **12a** from amine **17** and aldehyde **11** and successfully deprotected it to form compound **1a**. This approach was then applied to the synthesis of compounds **1b**−**e** to afford the corresponding bis-trifluoroacetate or bishydrochloride salts. The second successful

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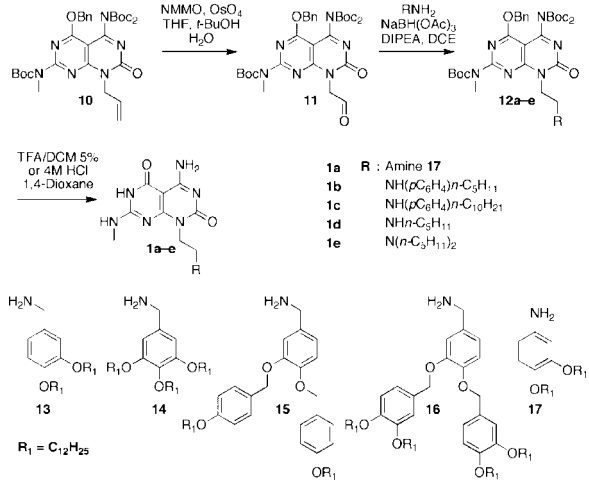
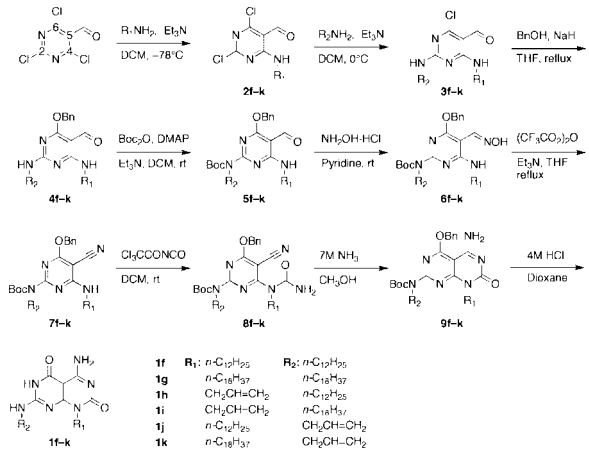
SCHEME 1. First Strategy To Derivatize the G∧C Base[a]



[a] Aldehyde **12** and amines **14**−**18** were prepared according to reported procedures.

SCHEME 2. Second Strategy To Derivatize the G∧C Base



approach consisted in incorporating the alkyl chains early in the synthesis as shown in Scheme 2.

Four types of hydrophobic G∧C derivatives were synthesized. The first with an arylalkylamino chain (**1a**−**c**), the second with one or two C5 alkylamino chains (**1d**,**e**), the third with two C12 (or C18) alkyl chains (**1f**,**g**), and the fourth with one C12 (or C18) alkyl chain and an allyl group (**1h**−**k**). Compounds **1a**−**e** were prepared from aldehyde[1c] **11** in ca. 47% yield (two steps) via reductive amination with the appropriate amines, followed by acid hydrolysis of the Boc and Bn groups (Scheme 1). Compound **11** was prepared in eleven steps in multigram quantities according to a previously reported strategy.[1] Compounds **1f**−**k** were synthesized in nine steps from a common precursor (2,4,6-trichloropyrimidine-5-carbaldehyde) in 17−43% overall yield (81−91% average stepwise yield) (Scheme 2). The allyl group in compounds **1h**−**k** was introduced as a handle for further chemical derivatization.[1c] All compounds were characterized by NMR spectroscopy, HR-MS (ES-CI), and elemental analysis.[10]

Selective monosubstitution at position 4 of 2,4,6-trichloropyrimidine-5-carbaldehyde was achieved by S_NAr at −78 °C in the presence of 1 equiv of amine (Scheme 2). This selectivity was attributed to a directing effect resulting from either the formation of a stable hydrogen bond between the carbaldehyde and the amine or the formation of a transient carbinolamine species between the aldehyde and the amine. In agreement with these hypotheses, higher temperatures (0−25 °C), led to a mixture of 2- and 4-monosubstituted, as well as 2,4-disubstituted products.

The second S_NAr to form **3f**−**k** proceeded smoothly with 1 equiv of amine. When $R_1 = R_2$, 2 equiv of amine were added to 2,4,6-trichloropyrimidine-5-carbaldehyde at room temperature. In contrast with all other compounds, **3j** and **3k** were prepared from 4-allylamino-2,6-dichloropyrimidine-5-carbaldehyde, which was isolated as a byproduct of the first S_NAr.[10] The third S_NAr required the use of a stronger nucleophile (benzyl alkoxide) and elevated temperature (THF reflux) due to deactivation of the pyrimidine ring by the electron-donating alkylamines. The first Boc protection occurred selectively at the 2-amino position. The 4-amino group is less nucleophilic because the nitrogen is engaged in an intramolecular H-bond with the neighboring carbonyl group.

Conversion of aldehydes **5f**−**k** into the corresponding nitriles **7f**−**k** was carried out in two steps. Aldehydes **5f**−**k** were first converted to the corresponding oximes and then, depending on the nature of the R groups, they were dehydrated using either TFAA,[11] carbonyldiimidazole,[12] or trichlorotriazine,[13] under basic conditions.

Treatment of **7f**−**k** with the more stable *N*-trichloroacetyl isocyanate or with *N*-(chlorocarbonyl) isocyanate resulted in mixed ureas **8f**−**k**. The former had to be used in large excess (up to 4 equiv) to drive the reaction to completion in a reasonable period of time because of its lower reactivity. *N*-(Chlorocarbonyl) isocyanate on the other hand, was used in stochiometric amounts. However, this reagent must be freshly distilled and used under strictly anhydrous conditions as it decomposes and releases HCl in sufficient quantities to induce Boc deprotection. Bicyclic compounds **9f**−**k** were obtained in excellent yield upon basic work up, or treatment of the crude product **8f**−**k** with concentrated ammonia in methanol. Final deprotection in 4 M HCl/dioxane yielded target compounds **1f**−**k** in 98% average yield as monohydrochloride salts. It is particularly noteworthy that all intermediate compounds in the synthesis of **1f** could be isolated by selective precipitation in methanol (i.e., no chromatography). We anticipate that **1g**−**k** and the compounds leading to them could also be subjected to the same selective precipitation method.

To demonstrate the success of our strategy, **1f** was chosen as a model compound to investigate the self-assembly and hydrophobic character of this new family of G∧C derivatives. Compound **1f** is soluble in hexane up to ca. 0.5 g/L, which achieves the primary goal of making the RNTs compatible with nonpolar organic solvents. Tapping mode atomic force microscopy (TM-AFM) imaging of a sample from a diluted solution (0.25 g/L, hexane) on mica resulted in networks of RNTs comprised of single nanotubes (Figure 1A). Scanning electron microscopy (SEM) images (Figure 1B) are consistent with AFM revealing high aspect ratio nanostructures with an outer diameter of 4.8 ± 0.5 nm, in agreement with the calculated value of 4.9 nm.

The hydrophobicity of the RNTs was investigated using a pendant water drop method as a film balance[14] by means of axisymmetric drop shape analysis profile (ADSA-P). ADSA-P

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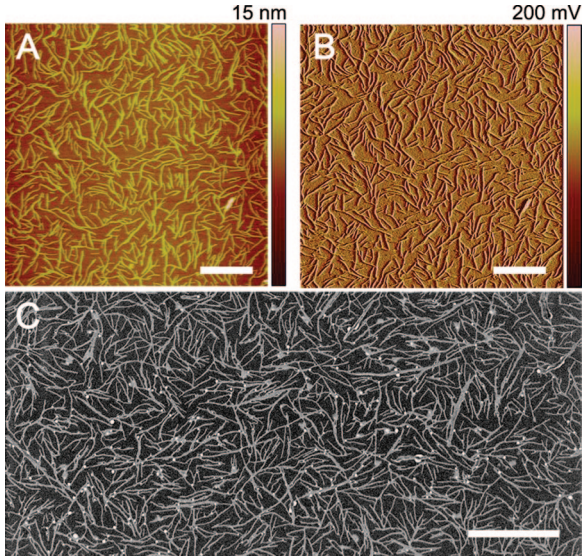

FIGURE 1. Tapping mode AFM height (A) and amplitude images (B) on mica and SEM image of **1f** on carbon-coated copper grid (C). **1f** was dissolved in hexane (0.25 g/L), sonicated, heated to the boiling point, and then aged for 1 h at room temperature prior to imaging. Scale bars = 1 μm.

is a precise method to determine liquid-fluid interfacial tensions and contact angles.[15] Assuming that the experimental drop is Laplacian and axisymmetric, the surface tension, drop volume, surface area, and radius of curvature can be computed from an image of the drop. Fitting the shape of the experimental drop to a theoretical drop profile according to Laplace equation of capillarity gives the correct surface/interfacial tension from which the contact angle can be determined by a numerical integration of Laplace equation.

A known amount of RNTs in hexane was first deposited onto a water pendent drop. As the hexane evaporated, the RNTs were anticipated to migrate to the air−water interface. If RNTs remain on the water surface, variations of droplet surface area at constant number of molecules would cause both the surface tension and surface pressure to change. This in turn was anticipated to validate the hydrophobic nature of the RNTs if the surface tension of the drop was affected. Initially a drop of water, hanging from a needle was prepared and the surface tension of pure water was measured to rule out the presence of contaminants. Thus, the addition of 1 μL of pure hexane to the water drop altered the surface tension but upon evaporation of hexane (within 6 s) the water surface tension returned to its initial value (Figure 2A).

When 1 μL of the RNT solution in hexane (0.5 g/L) was carefully added to the water drop (Figure 2B), the surface tension of water decreased instantaneously from ca. 72 to 45.5 mJ/m^2, stabilizing at 47.5 mJ/m^2 after hexane evaporation. The change in surface tension is presumably due to the presence of RNTs at the air−water interface. By altering the surface area of the drop, which can be performed by gradual pumping and suction of the water drop from the needle, surface tension variations can be measured directly from images of the drop profile using ADSA-P. As the surface area increases (area A), the RNTs spread more at the air−water interface and water regains some of its natural surface tension. As long as the surface area is

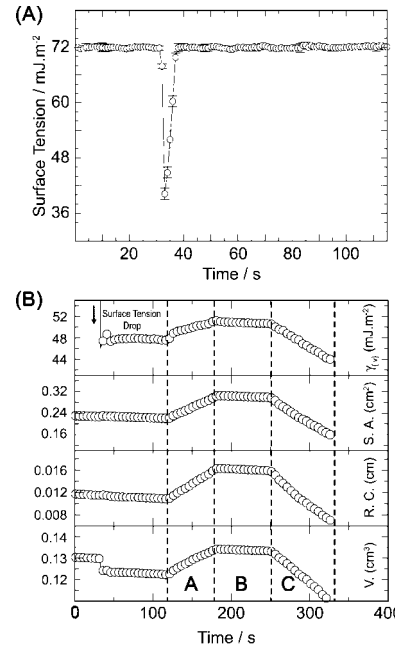

FIGURE 2. Effect of hydrophobic RNT **1a** on water surface tension. (A) Variation of surface tension of water after adding microliter volume of pure hexane. (B) Variation of surface tension of pure water containing **1a** (0.5 g/L in hexane). Abbreviations: V = volume, R.C. = radius of curvature, S.A. = surface area.

constant (area B), the surface tension remains constant. By decreasing the surface area (area C), the surface tension starts decreasing and Langmuir−Blodgett films of RNTs start forming. When the surface area was decreased further, the surface tension reached its lower limit (end of area C) suggesting that the RNTs have formed a tightly packed film at the air−water interface. If RNTs had affinity for water, they would have migrated into the water bulk at high surface pressure. The reduction in the surface tension as the drop area decreases or surface concentration increases suggest that an RNT film was formed at the air−water interface and that RNTs formed from **1f** are indeed hydrophobic in nature.

In summary, 11 G∧C derivatives bearing long chain alkyl substituents were synthesized and characterized. Target compounds **1a**−**k** were soluble in low polarity organic solvents, which achieves the main goal of this work. In particular, **1f**−**k** showed higher solubility (ca. 3.0 g/L) in nonpolar solvents (e.g., chloroform, hexane, and dodecane) relative to **1a**−**e** (ca. 0.05 g/L). Due to the presence of a protonated nitrogen in the latter series, these compounds are more soluble in polar organic solvents (ca. 8.0 g/L) such as dimethyl sulfoxide, dimethyformamide, and nitromethane.

Preliminary studies on compound **1f** showed the formation of RNTs in hexane and Langmuir−Blodgett films at the air−water interface. Our next step is to investigate the self-assembly properties of **1a**−**k** in greater detail. This work is currently in progress and will be reported in due course.

Experimental Section

Typical Reductive Amination Procedure. Compound **11** (0.51 g, 0.8 mmol) and 4-pentylaniline (0.17 mL, 0.96 mmol) were dissolved in 1,2-DCE (30 mL) with stirring under argon. DIEA (0.17 mL, 0.98 mmol) was then added, and the mixture was allowed to stir for 5 d before adding $NaBH(OAc)_3$ (242 mg, 1.25 mmol). After 49 h, the reaction was quenched with distilled water (10 mL). The organic layer was removed, and the aqueous layer was washed

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with CH_2Cl_2 (2 × 15 mL). The organic layers were combined and washed with distilled water (2 × 15 mL), 10% aqueous citric acid (15 mL), and brine (15 mL). The solvent was then removed (Rotavap), and the orange solid was dried in vacuo for 30 min. Compound **12b** (0.53 g, 91%) was obtained as a yellow solid after silica gel flash chromatography (10−30% EA/Hex). ^{1}H NMR (400 MHz, $CDCl_3$):[10] δ (ppm) 7.43 (m, 2H, $C_{12}H/C_{16}H$), 7.38−7.30 (m, 3H, $C_{13-15}H$), 6.93 (m, 2H, $C_{28}H/C_{36}H$), 6.56 (m, 2H, $C_{29}H/C_{35}H$), 5.56 (s, 2H, $C_{10}H$), 4.62 (t, 2H, C_6H), 3.54 (t, 2H, C_7H), 3.44 (s, 3H, C_9H), 2.45 (t, 2H, $C_{37}H$), 1.60 (s, 9H, $C_{19}H$), 1.53 (m, 2H, $C_{38}H$), 1.31 (s, 18H, $C_{23}H$ and $C_{26}H$), 1.36−1.21 (m, 4H, $C_{39}H$ and $C_{40}H$), 0.87 (t, 3H, $C_{41}H$). ^{13}C NMR (400 MHz, $CDCl_3$):[10] δ (ppm) 165.7 (C_4), 161.3 (C_1, C_2, C_3, C_5 or C_{20}), 160.9 (C_1, C_2, C_3, C_5 or C_{20}), 160.5 (C_3 or C_5), 156.0 (C_2 or C_{20}), 152.4 (C_{17}), 149.3 (C_{21}/C_{24}), 145.8 (C_{27}), 134.8 (C_{11}), 131.7 (C_{34}), 128.9 (C_{28}/C_{36}), 128.6 (C_{13}/C_{15} or C_{14}), 128.5 (C_{13}/C_{15} or C_{14}), 128.2 (C_{12}/C_{16}), 112.7 (C_{29}/C_{35}), 93.0 (C_3 or C_5), 83.8 (C_{22}/C_{25}), 70.1 (C_{10}), 42.8 (C_6 and C_7), 34.9 (C_9 and C_{33}), 34.8 (C_{34}), 34.7, 31.5 (C_{35}), 31.4 (C), 28.1 (C_{19}), 27.8 (C_{23}/C_{26}), 22.5 (C_{36}), 14.0 (C_{37}). Positive ESI-MS: calcd for ($C_{42}H_{57}N_6O_8 + H^+$) *m/z* 788.4, obsd 788.8.

General Procedure for 4f−k. Benzyl alcohol (0.99 g, 0.91 mL, 8.8 mmol) was added to a stirred suspension of NaH (95%, 0.84 g, 35.8 mmol) in THF (10 mL) at rt under N_2 atmosphere. After 15 min the solution was cooled to 0 °C, then a solution of compound **3f** (4.48 g, 8.80 mmol) in THF (40 mL) was added. The mixture was allowed to warm to rt, then it was refluxed for 24 h. The mixture was then cooled to 0 °C and carefully quenched with saturated NH_4Cl (10 mL). The solvent was removed (Rotavap), and the residual solid was dissolved in Et_2O, washed with dH_2O (100 mL) and brine (50 mL), and dried over anhydrous Na_2SO_4. Filtration, evaporation of the solvent (Rotovap) followed by silica gel chromatography (0−5% EA/Hex) yielded **4f** as a white solid (4 g, 79%). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm):[10] 9.82 (HC_5, s, 1H), 9.03 ($HNC_{1''}$, major, t, J = 4.2 Hz, 1H), 7.42−7.22 ($HNC_{1'}$ overlapping with HC_8−HC_{12}, 6H), 5.40 (HC_6, s, 2H), 3.41, 3.28 ($HC_{1'}$, dt, J = 13.2 Hz, J = 5.6 Hz, 2H; $HC_{1''}$, dt, J = 13.2 Hz, J = 5.6 Hz, 2H), 1.52 ($HC_{2'}$ + $HC_{2''}$, m, 4H), 1.30−1.20 ($HC_{3'}$-$HC_{11'}$ + $HC_{3''}$-$HC_{11''}$, m, 32H), 0.83 ($HC_{12'}$ + $HC_{12''}$, t, J = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm):[10] 185.8 (C_5), 171.5, 163.5, 162.3 (C_1, C_2, C_4), 136.7 (C_7), 128.5, 127.9, 127.7 (C_{8-12}), 92.8 (C_3), 67.3 (C_6), 41.4, 40.4 ($C_{1'}$, $C_{1''}$), 31.9−22.7 ($C_{2'}$−$C_{11'}$, $C_{2''}$−$C_{11''}$), 14.1 ($C_{12'}$, $C_{12''}$). FTIR (cm^{-1}): 3331, 3258, 2953, 2912, 2847, 1631, 1593, 1576, 1539, 1518, 1208, 1111. HRMS (ESI): calcd for ($C_{36}H_{60}N_4O_2$ +H^+) *m/z* 465.3355, obsd *m/z* 465.3354.

General Procedure for 7f−k. Compound **6f** (11.0 g, 15.8 mmol) was dissolved in THF (130 mL) and the solution cooled to 0 °C in an ice bath. After addition of Et_3N (7 mL, 50.2 mmol) to the solution, TFAA (4.4 mL, 31.6 mmol) was added over 30 min. After being stirred for 15 min, the mixture was allowed to warm to rt, and then it was refluxed for 5 h. After the mixture was cooled to rt, the reaction was quenched with dH_2O and the solvent was evaporated under reduced pressure (rotavap). The residual solid was dissolved in ethyl acetate (600 mL), washed with dH_2O (3 × 50 mL), 5% aqueous $NaHCO_3$ (2 × 50 mL) and brine (50 mL), and then dried over anhydrous Na_2SO_4. The solvent was removed (rotovap), and the residual solid was precipitated in CH_3OH to yield **7f** as a white solid (10.2 g, 92% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):[10] 7.45−7.26 (m, HC_8−HC_{12}, 5H), 5.45 (HC_6, s, 2H), 5.36 ($HNC_{1''}$, t, J = 5.2 Hz, 1H), 3.84 ($HC_{1'}$, m, 2H), 3.48 ($HC_{1''}$, dt, J_1 = 7.2 Hz, J_1 = 13.2 Hz, 2H), 1.63−1.57 ($HC_{2'}$ + $HC_{2''}$, m, 4H), 1.54 (HC_{15}, s, 9H), 1.34−1.24 ($HC_{3'}$-$HC_{11'}$ + $HC_{3''}$-$HC_{11''}$, m, 32H), 0.89 ($HC_{12'}$ + $HC_{12''}$, t, J = 7.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm):[10] 170.2 (C_4), 164.1, 160.7 (C_1, C_2), 153.3 (C_{13}), 136.5 (C_7), 128.4, 128.0, 127.8 (C_{8-12}), 115.0 (C_5), 82.1 (C_{14}), 68.5 (C_3), 68.2 (C_6), 47.3 ($C_{1'}$), 41.0 ($C_{1''}$), 31.8−22.5 ($C_{2'}$−$C_{11'}$, $C_{2''}$−$C_{11''}$), 28.2 (HC_{15}), 14.0 ($C_{12'}$, $C_{12''}$). FTIR (cm^{-1}): 3303, 3176, 2915, 2849, 2221, 1751, 11706, 1610, 1587, 1214, 1125. HRMS (ESI): calcd for ($C_{41}H_{67}N_5O_3$ +H^+) *m/z* 678.5317, obsd *m/z* 678.5313.

General Procedure for 8f−k. To a solution of **7f** (0.41 g, 0.6 mmol) in DCM (50 mL) was added *N*-trichlorometylcarbonyl isocyanate (0.23 g, 0.14 mL, 1.2 mmol) at 0 °C under N_2 atmosphere. After being stirred for 1 h at 0 °C, the mixture was allowed to warm to rt and was stirred for an additional 48 h. The reaction mixture was cooled to 0 °C and carefully quenched with dH_2O (10 mL, exothermic reaction!) followed by 5% aqueous $NaHCO_3$ (10 mL). The product was extracted with DCM (300 mL), and the organic layer was washed with dH_2O (2 × 50 mL) and brine (100 mL) and dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent (rotovap), the residual mixture was used in the next step without further purification.

General Procedure for 1f−k. Compound **9f** (0.15 g, 0.02 mmol) was dissolved in a 4 M solution of HCl in dioxane (4 mL), and the mixture was refluxed for 2 h. The white precipitate formed was filtered, washed with DCM (5 × 10 mL), and dried on a filter. Compound **1f** was obtained as a white solid (0.11 g, quantitative). ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ (ppm):[10] 12.2−11.2 (H_C, br s, 1H), 9.08 (H_A, s, 1H), 8.34 (H_B, s, 1H), 8.16 (H_D, s, 1H), 4.04 ($HC_{1'}$, t, J = 7.5, 2H), 3.43 ($HC_{1''}$, dt, J_1 = J_2 = 6.5 Hz, 2H), 1.68−1.58 ($HC_{2'}$ + $HC_{2''}$, m, 4H), 1.38−1.24 ($HC_{3'}$−$HC_{11'}$ + $HC_{3''}$−$HC_{11''}$, m, 36H), 0.88 ($HC_{12'}$ + $HC_{12''}$, t, J = 6.5 Hz, 6H). ^{1}H NMR (300 MHz, $CDCl_3$, 40 °C) δ (ppm):[10] 12.7−12.2 (H_C, br. s, 1H), 9.35 (H_A, s, 1H), 9.04, 9.01 (H_B, H_D, 2H), 4.13 ($HC_{1''}$, br s, 2H), 3.50 ($HC_{1''}$, br s, 2H), 1.80−1.60 ($HC_{2'}$ + HC″, m, 4H), 1.40−1.25 ($HC_{3'}$−$HC_{11'}$ + $HC_{3''}$−$HC_{11''}$, m, 36H), 0.90 ($HC_{12'}$ + $HC_{12''}$, t, J = 6.8 Hz, 6H). ^{1}H NMR (500 MHz, CF_3CO_2D) δ (ppm):[10] 4.50 ($HC_{1''}$, br s, 2H), 3.87 ($HC_{1''}$, br s, 2H), 2.05−1.95 ($HC_{2'}$ + $HC_{2''}$, m, 4H), 1.63−1.40 ($HC_{3'}$−$HC_{11'}$ + $HC_{3''}$−$HC_{11''}$, m, 36H), 1.05 ($HC_{12'}$ + $HC_{12''}$, t, J = 5.9 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm):[10] 165.8 (C_5), 162.8 (C_2), 157.8 (C_4), 156.8 (C_1), 151.8 (C_{16}), 84.8 (C_3), 46.5 ($C_{1''}$), 44.9 ($C_{1'}$), 33.8−24.3 ($C_{2'}$−$C_{11'}$, $C_{2''}$-$C_{11''}$), 14.6 ($C_{12'}$, $C_{12''}$) (assignments were made based on HMBC/HMQC spectra). FTIR (cm^{-1}): 3322, 3174, 2954, 2847, 1715, 1667, 1612, 1544. Anal. Calcd for $C_{30}H_{54}N_6O_2$−HCl: C, 63.56; H, 9.79; N, 14.83; Cl, 6.25. Found: C, 63.20; H, 9.63; N, 14.71; Cl, 6.21. HRMS (ESI): calcd for ($C_{42}H_{68}N_6O_4$ + H^+) *m/z* 531.4381, obsd *m/z* 531.4383.

Tapping Mode Atomic Force Microscopy. Samples for AFM imaging were prepared in a Class 10000 Clean Room by spin coating (Cookson G3-8 Desk-Top Precision Spin Coating System) 25 μL of a 0.25 g/L solution of the RNTs on 1 × 1 cm^2 freshly peeled Mica grade V-4 (SPI supplies) substrates. AFM measurements were performed in tapping mode (TM-AFM) at a scan rate of 2 Hz per line using a Digital Instruments/Veeco Instruments MultiMode Nanoscope IV equipped with an E scanner. Silicon cantilevers (MikroMasch USA, Inc.) with spring constants of 40 N/m were used.

Electron Microscopy. The samples were prepared by placing a carbon-coated 400-mesh copper grid on a droplet of **1f** (0.25 g/L) for 5 s. The grid was then blotted and air-dried prior to imaging. SEM images were obtained without staining at 5−30 kV accelerating voltage and a working distance of 3.0−6.0 mm on a high resolution Hitachi S-4800 cold field emission SEM.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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