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Construction of macrocyclic structure using conformational properties of secondary and tertiary aromatic amides

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Abstract—A large macrocyclic compound with six *para*-phenylene rings and six amide moieties, which are alternately secondary and tertiary, was synthesized. In a stepwise synthesis, the final cyclization step was successful because a combination of three tertiary amides, which prefer a cis conformation, and two linear secondary amides would arrange both amino and carboxyl ends close to each other, while various sizes of macrocyclic compounds including the target cyclic trimer were generated in one-pot synthesis where three secondary amide bonds were formed.

Aromatic amides have been utilized as versatile fragments to construct frameworks that have various functions such as chemical sensing, conformational switching or biological activities based on molecular recognition.[1–3] Especially, conformational alternation by N-alkylation of aromatic amides from trans[4] to cis[5–7] gives folded structures to such molecules (Fig. 1). In the course of our study on the stereochemistry of aromatic amides, we found that a cyclic structure can be easily constructed using conformational alternation by the *N*-alkyl group on the amide nitrogen. For example,

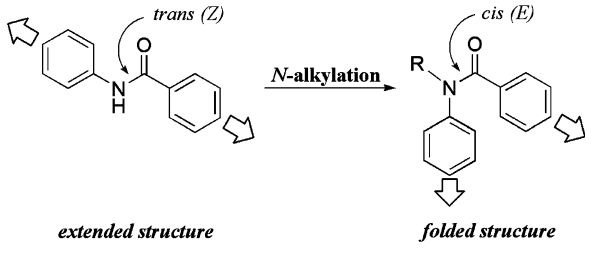

Figure 1. Conformational alternation by N-alkylation of aromatic amides.

4- or 3-methylaminobenzoic acid coupled with themselves by a one-pot reaction using tetrachlorosilane[8,9] or dichlorotriphenylphosphorane[10] effectively gives cyclized aromatic amides. On the other hand, the secondary amide moiety makes a molecule having an extended structure, which would enlarge the cyclic structure when the secondary amide is inserted into the cyclic aromatic amide. Furthermore, the secondary amide moiety, which can form a hydrogen bonding, would provide a cavity that interacts with various ligands to the macrocyclic compounds. We report the synthesis of a large cyclic aromatic amide that has secondary and tertiary amides alternately.

Initially, we designed macrocyclic aromatic amide **3** with methyl groups for R (Scheme 1) and tried one-pot macrocyclization from aromatic amino acid **1** using dichlorotriphenylphosphorane in 1,1,2,2-tetrachloroethane at 120 °C.[10,11] White powder which showed the expected molecular weight (757: $[M+H]^+$) was obtained (60% yield) but was hardly soluble in various polar or nonpolar solvents. Next, another aromatic amino acid **2** having a hydrophobic *n*-decyl group was prepared and coupled under the same conditions. The resulting mixture showed 1157, 1536, 1914, 2292, 2670, 3050 ($[M+Na]^+$: 3–8mer of **2**, respectively) in FAB Mass spectrum, but complete isolation was difficult because of the presence of the isomers and many side products.

Keywords: Cyclization; Secondary amide; Tertiary amide; Aromatic amide; Cyclic amide.
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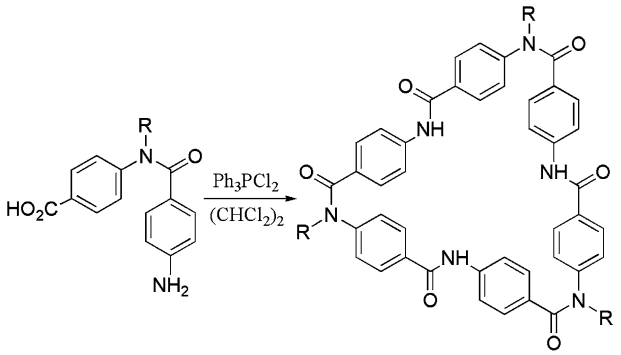
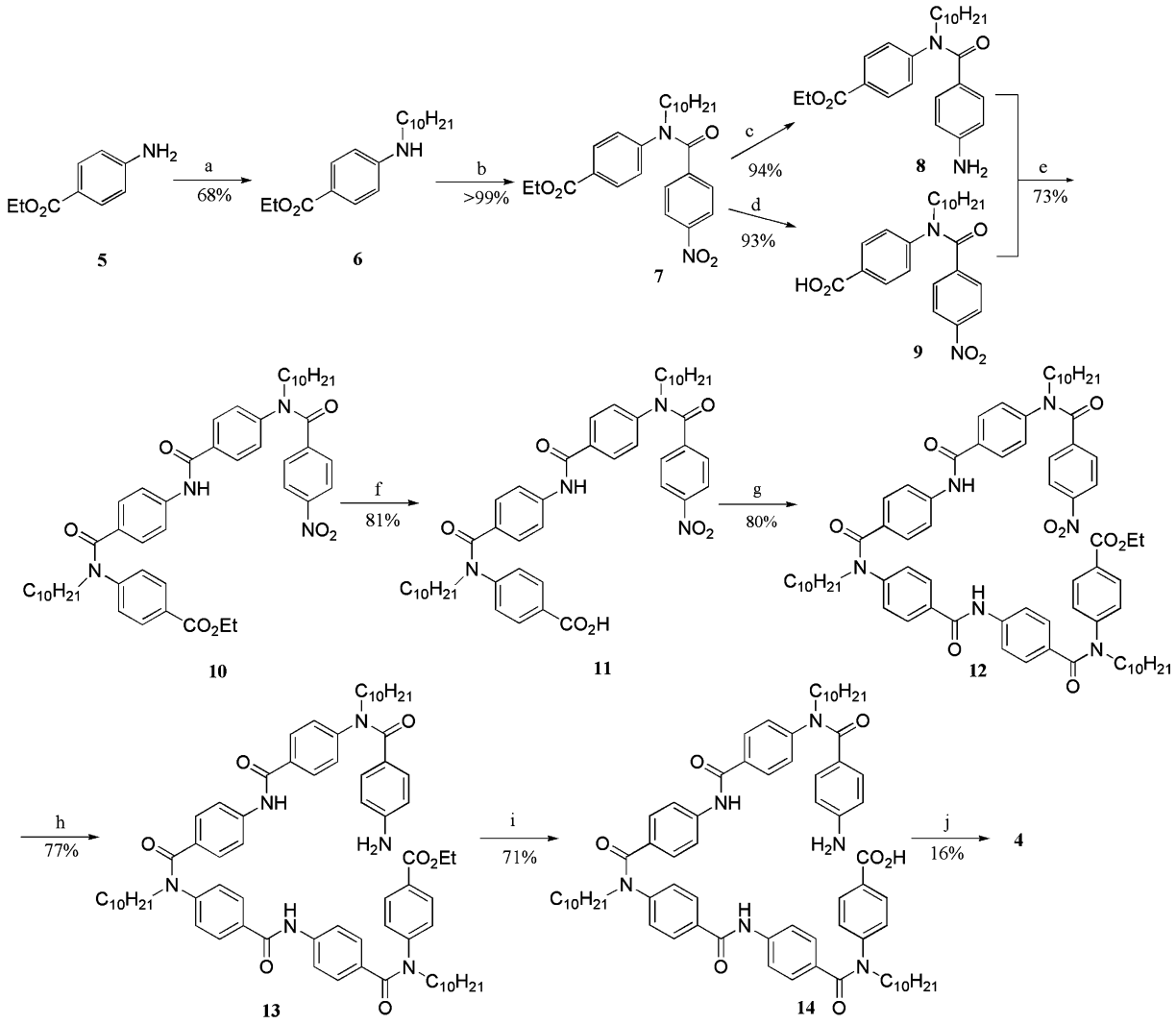


1 R = CH_3
2 n-$C_{10}H_{21}$
3 R = CH_3
4 n-$C_{10}H_{21}$

Scheme 1. One-pot macrocyclization from aromatic amino acid.

So we synthesized the macrocyclic compounds **4** from ethyl 4-aminobenzoate **5** stepwise as shown in Scheme 2.[14] Direct monoalkylation of an aromatic amino group was achieved using 0.5 equiv of iododecane[12] because unreacted and didecylated amine could be easily separated by standard silica gel column chromatography (eluent: ethyl acetate–hexane = 1:6). After 4-nitrobenzoylation, compound **7** was converted to amine **8** by hydrogenation over Pd/C, and to carboxylic acid **9** by hydrolysis. A key amidation reaction of **8** and **9** was successful by using dichlorotriphenylphosphorane in high yield (73%). Oligomer **10** was hydrolyzed, followed by amidation with **8** by dichlorotriphenylphosphorane to give oligomer **12**. Reduction of the nitro group followed by hydrolysis gave the chained aromatic amino acid **14** having six phenylene groups.

The final cyclization reaction (0.03 M of **14**) was also achieved using dichlorotriphenylphosphorane to give the target macrocyclic aromatic amide **4**.[15] The yield was lower than expected (16%), but a compound having a double mass number (6mer)[16] was obtained in lower yield (12%) and a complex of more polymerized compounds was obtained (23% yield). A possible reason



Scheme 2. Reagents and conditions: (a) n-$C_{10}H_{21}I$, HMPA, 120 °C, 2.5 h; (b) 4-nitrobenzoylchloride, pyridine, rt, 1.5 h; (c) 10% Pd/C, H_2, EtOH, rt, 2h; (d) 4 N NaOH, EtOH, rt, 45 min; (e) Ph_3PCl_2, $CHCl_3$, reflux, 3 h; (f) 4 M NaOH, EtOH, rt, 30 min; (g) **8**, Ph_3PCl_2, $CHCl_3$, reflux, 2 h; (h) 10% Pd/C, H_2, EtOH, rt, 14 h; (i) 4 M NaOH, EtOH, rt, 1.5 h; (j) Ph_3PCl_2, $CHCl_3$, reflux, 8.5 h.

why the yield of the macrocyclized compound was lower than that in the one-pot cyclization of 4-methylaminobenzoic acid by dichlorotriphenylphosphorane[10] could be because the oligomeric amino acid **14** right before the macrocyclization could exist in various conformation due to phenylene-N or phenylene-CO rotations. A few conformations out of the many possible conformations should be preferable to the cyclization, contrary to that one conformation (the terminal two benzene rings located in syn conformation) out of two possible conformations (syn or anti) are preferable in the final amidation step in the one-pot cyclization of 4-methylaminobenzoic acid.

In the ^{1}H NMR spectrum of macrocyclic compound **4**, four slightly broadened doublet aromatic protons were observed (δ 7.04, 7.18, 7.46, 7.73). This shows the dynamic behavior of **4** has C_{3h} symmetry in the NMR timescale at room temperature. Three *N*-decylamide groups would have adopted cis (*E*) conformation since a ROESY correlation was observed between aromatic protons ortho to the decyl-*N* and aromatic protons ortho to the carbonyl of NH-amide, and no ROESY correlation was observed between protons ortho to the NH and protons ortho to the carbonyl of *N*-decylamide. Therefore, macrocyclic compound **4** existed, as expected, in a conformation with a large triangle (Scheme 1), due to a cis-preference of the tertiary amide and a trans-preference of the secondary amide.

Preliminary conformational analysis was performed on 'SPARTAN'02 for Linux' program.[13] The most promising structure among AM1-minimized conformations of macrocyclic compound **3** (after conformational search using Monte Carlo method on MMFF94 force field) is shown in Figure 2. This conformation, where all the amide planes are located in the same direction, is corresponding to the symmetrical ^{1}H NMR spectrum of **3** due to local conformational equilibria including twist of phenylene rings and amide bondings.

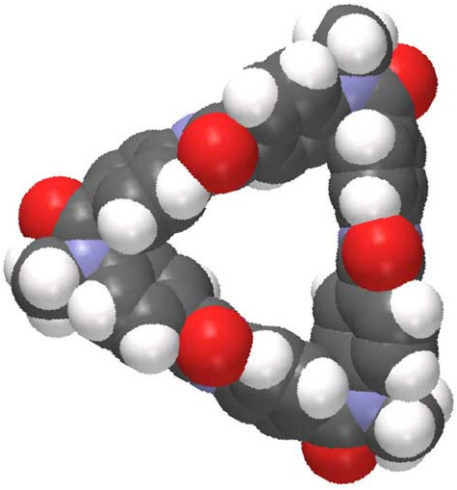


Figure 2. AM1-optimized structure of macrocyclic amide **3** starting from the most stable conformation obtained by conformational search calculation using MMFF94 force field.

In conclusion, we achieved a synthesis of a large cyclic aromatic amide that has secondary and tertiary amides alternately, by utilizing their conformational properties. This strategy can produce macrocyclic compounds with various sizes of cavities. Details of the dynamic behavior and inclusion properties of the macrocyclic aromatic amide **4** are now under study.

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13. SPARTAN'02 for Linux: Wavefunction, Inc.
14. Spectral data of compound **6**–**14**. Compound **6**: White powder, mp 71 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (3H, t, $J = 7.0$ Hz), 1.20–1.45 (14H, br m), 1.36 (3H, t, $J = 7.0$ Hz), 1.62 (2H, tt, $J = 7.0$, 7.0 Hz), 3.15 (2H, t, $J = 7.0$ Hz), 4.13 (1H, br s), 4.31 (2H, t, $J = 7.0$ Hz), 6.54 (2H, ddd, $J = 9.0$, 2.0, 2.0 Hz), 7.86 (2H, ddd, $J = 9.0$, 2.0, 2.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 14.4, 22.6, 27.0, 29.3, 29.3, 29.4, 29.5, 29.5, 31.9, 43.4, 60.1, 111.3, 118.4, 131.5, 152.0, 166.9. MS (DI-EI) $m/z = 305$ [M^+]. Anal. Calcd for $C_{19}H_{31}NO_2$: C, 74.71; H, 10.23; N, 4.59. Found: C, 74.47; H, 10.12; N, 4.70. Compound **7**: Pale yellow amorphous. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (3H, t, $J = 7.0$ Hz), 1.18–1.40 (14H, br m), 1.36 (3H, t, $J = 7.0$ Hz), 1.61 (2H, tt, $J = 7.0$, 7.0 Hz), 3.95 (2H, t, $J = 7.0$ Hz), 4.34 (2H, q, $J = 7.0$ Hz), 7.06 (2H, ddd, $J = 9.0$, 2.0, 2.0 Hz), 7.43 (2H, ddd, $J = 9.0$, 2.0, 2.0 Hz), 7.92 (2H, ddd, $J = 9.0$, 2.0, 2.0 Hz), 8.03 (2H, ddd, $J = 9.0$, 2.0, 2.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 14.2, 22.6, 26.8, 27.7, 29.2, 29.5, 31.8, 50.4, 61.3, 142.1, 146.5, 148.1, 123.2, 127.4, 129.2, 129.5, 130.8, 165.4, 168.0. MS (DI-EI) $m/z = 454$ [M^+]. Anal. Calcd for $C_{26}H_{34}N_2O_5$: C, 68.70; H, 7.54; N, 6.16. Found: C, 68.62; H, 7.61; N, 6.29. Compound **8**: White powder, mp 56 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (3H, t, $J = 7.0$ Hz), 1.18–1.40 (14H, br m), 1.36 (3H, t, $J = 7.0$ Hz), 1.56–1.66 (2H, br m), 3.79 (2H, br s), 3.90 (2H, t, $J = 7.0$ Hz), 4.34 (2H, q, $J = 7.0$ Hz), 6.40 (2H, ddd, $J = 9.0$, 2.0, 2.0 Hz), 7.06 (2H, ddd, $J = 9.0$, 2.0, 2.0 Hz), 7.11 (2H, ddd, $J = 9.0$, 2.0, 9.0 Hz), 7.89 (2H, ddd, $J = 9.0$, 2.0, 2.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 14.3, 22.6, 27.0, 27.9, 29.2, 29.3, 29.5, 29.5, 31.8, 50.6, 61.0, 113.6, 123.6, 126.8, 127.5, 130.4, 131.1, 148.2, 148.8, 165.9, 170.2. MS (FAB) $m/z = 425$ [M+H]$^+$. Anal. Calcd for $C_{26}H_{36}N_2O_3$: C, 73.55; H, 8.55; N, 6.60. Found: C, 73.41; H, 8.54; N, 6.73. Compound **9**: White powder, mp 108 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (3H, t, $J = 7.0$ Hz), 1.18–1.40 (14H, br m), 1.57–1.68 (2H, br m), 3.97 (2H, t, $J = 7.0$ Hz), 7.11 (2H, ddd, $J = 9.0$, 2.0, 2.0 Hz), 7.44 (2H, ddd, $J = 9.0$, 2.0, 2.0 Hz), 7.97 (2H, ddd, $J = 9.0$, 2.0, 2.0 Hz), 8.04 (2H, ddd, $J = 9.0$, 2.0, 2.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.6, 26.8, 27.7, 29.2, 29.5, 31.8, 50.5, 123.3, 127.4, 127.9, 129.5, 131.5, 141.8, 147.4, 148.2, 168.1, 170.2. MS (DI-EI) $m/z = 426$ [M^+]. Anal. Calcd for $C_{24}H_{30}N_2O_5$: C, 67.59; H, 7.09; N, 6.57. Found: C, 67.30; H, 6.90; N, 6.67. Compound **10**: Yellow amorphous. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (6H, t, $J = 7.0$ Hz), 1.18–1.40 (28H, br m), 1.36 (3H, t, $J = 7.0$ Hz), 1.55–1.65 (4H, br m), 3.92 (2H, t, $J = 7.0$ Hz), 3.94 (2H, t, $J = 7.0$ Hz), 4.33 (2H, q, $J = 7.0$ Hz), 7.06 (2H, ddd, $J = 9.0$, 2.0, 2.0 Hz), 7.10 (2H, ddd, $J = 9.0$, 2.0, 2.0 Hz), 7.26 (2H, ddd, $J = 9.0$, 2.0, 2.0 Hz), 7.41 (2H, ddd, $J = 9.0$, 2.0, 2.0 Hz), 7.43 (2H, ddd, $J = 9.0$, 2.0, 2.0 Hz), 7.72 (2H, ddd, $J = 9.0$, 2.0, 2.0 Hz), 7.81 (1H, br s), 7.89 (2H, ddd, $J = 9.0$, 2.0, 2.0 Hz), 8.03 (2H, ddd, $J = 9.0$, 2.0, 2.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 14.3, 22.6, 26.8, 26.9, 27.7, 27.8, 29.2, 29.3, 29.5, 31.8, 50.5, 50.5, 61.1, 119.0, 123.3, 127.1, 127.8, 128.3, 128.4, 129.5, 130.0, 130.5, 131.9, 133.2, 139.0, 142.0, 145.8, 147.8, 148.1, 164.1, 165.7, 168.0, 169.5. MS (FAB) $m/z = 833$ [M+H]$^+$. Anal. Calcd for $C_{50}H_{64}N_4O_7$: C, 72.09; H, 7.74; N, 6.73. Found: C, 71.96; H, 7.79; N, 6.72. Compound **11**: Pale yellow amorphous. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (6H, t, $J = 7.0$ Hz), 1.18–1.38 (28H, br m), 1.58–1.68 (4H, br m), 3.94 (4H, br t, $J = 7.0$ Hz), 7.09 (4H, d, $J = 9.0$ Hz), 7.27 (2H, d, $J = 9.0$ Hz), 7.42 (4H, dd, $J = 9.0$, 2.0 Hz), 7.72 (2H, d, $J = 9.0$ Hz), 7.87 (1H, br s), 7.93 (2H, d, $J = 9.0$ Hz), 8.0 (2H, d, $J = 9.0$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.6, 26.8, 26.9, 27.7, 27.8, 29.2, 29.3, 29.5, 31.8, 50.6, 119.0, 123.2, 127.0, 127.2, 127.8, 128.4, 129.5, 130.1, 131.2, 131.7, 133.2, 139.2, 142.0, 145.8, 148.1, 148.6, 164.3, 168.0, 169.6, 169.6. MS (FAB) $m/z = 805$ [M+H]$^+$. HRMS (FAB) Calcd for $C_{48}H_{60}N_4O_7Na$ [M+Na]$^+$: 827.4360. Found: 827.4360. Compound **12**: Pale yellow amorphous. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.83–0.89 (9H, m), 1.18–1.38 (42H, br m), 1.36 (3H, t, $J = 7.0$ Hz), 1.54–1.65 (6H, br m), 3.86–3.96 (6H, br m), 4.33 (2H, q, $J = 7.0$ Hz), 7.07 (4H, d, $J = 8.5$ Hz), 7.09 (2H, d, $J = 8.5$ Hz), 7.23 (2H, d, $J = 8.5$ Hz), 7.26 (2H, d, $J = 8.5$ Hz), 7.36 (2H, d, $J = 8.5$ Hz), 7.42 (2H, d, $J = 8.5$ Hz), 7.43 (2H, d, $J = 8.5$ Hz), 7.68 (2H, d, $J = 8.5$ Hz), 7.70 (2H, d, $J = 8.5$ Hz), 7.90 (2H, d, $J = 8.5$ Hz), 7.96 (1H, br s), 8.03 (2H, d, $J = 8.5$ Hz), 8.08 (1H, br s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 14.3, 22.6, 26.8, 26.9, 27.8, 27.8, 29.2, 29.3, 29.5, 31.8, 50.6, 50.6, 61.1, 118.9, 119.2, 123.3, 127.1, 127.5, 127.8, 128.2, 128.2, 128.4, 129.4, 129.9, 130.0, 130.5, 131.7, 131.9, 132.4, 133.1, 139.0, 139.3, 142.0, 145.8, 147.0, 147.9, 148.1, 164.4, 164.7, 165.7, 168.0, 169.5. MS (FAB) $m/z = 1211$ [M+H]$^+$. HRMS (FAB) Calcd for $C_{74}H_{94}N_6O_9Na$ [M+Na]$^+$: 1233.6980. Found: 1233.6962. Compound **13**: Pale yellow amorphous. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.83–0.90 (9H, m), 1.18–1.38 (42H, br m), 1.35 (3H, t, $J = 7.0$ Hz), 1.50–1.64 (6H, br m), 3.80–3.95 (8H, br m), 4.32 (2H, q, $J = 7.0$ Hz), 6.38 (2H, d, $J = 8.5$ Hz), 7.00 (2H, d, $J = 8.5$ Hz), 7.02 (2H, d, $J = 8.5$ Hz), 7.06 (2H, d, $J = 8.5$ Hz), 7.09 (2H, d, $J = 8.5$ Hz), 7.15 (2H, d, $J = 8.5$ Hz), 7.23 (2H, d, $J = 8.5$ Hz), 7.31 (2H, d, $J = 8.5$ Hz), 7.47 (2H, d, $J = 8.5$ Hz), 7.58 (2H, d, $J = 8.5$ Hz), 7.74 (2H, d, $J = 8.5$ Hz), 7.89 (2H, d, $J = 8.5$ Hz), 8.28 (1H, br s), 8.69 (1H, br s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 14.3, 22.6, 26.9, 26.9, 27.8, 28.1, 29.3, 29.3, 29.3, 29.3, 29.5, 29.5, 29.5, 31.8, 50.5, 50.6, 50.8, 61.1, 113.6, 119.0, 119.4, 123.6, 124.9, 127.1, 127.2, 127.5, 128.0, 128.2, 128.4, 129.7, 129.9, 130.5, 130.9, 131.4, 131.5, 131.7, 132.5, 139.2, 139.7, 146.9, 147.9, 147.9, 148.5, 164.8, 165.4, 165.7, 169.6, 169.7, 170.4. MS (FAB) $m/z = 1181$ [M+H]$^+$. HRMS (FAB) Calcd for $C_{74}H_{96}N_6O_7Na$ [M+Na]$^+$: 1203.7238. Found 1203.7263. Compound **14**: Pale yellow amorphous. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (9H, br t, $J = 7.0$ Hz), 1.12–1.35 (42H, br m), 1.49 (2H, br s), 1.58 (4H, br s), 3.74 (2H, br s), 3.89 (4H, br s), 6.42 (2H, br d), 6.88 (2H, br d), 6.94–7.06 (6H, br m), 7.07–7.16 (4H, br m), 7.30 (2H, br s), 7.43 (4H, br d), 7.80 (2H, br d), 7.90 (2H, br d), 8.84 (1H, br s), 9.60 (1H, br s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.6, 26.8, 26.9, 27.7, 27.8, 28.2, 29.2, 29.2, 29.3, 29.5, 29.5, 31.8, 50.3, 50.7, 51.2, 124.4, 127.0, 127.1, 127.3, 127.6, 128.1, 128.8, 129.4, 129.8, 130.4, 130.8, 130.8, 131.4, 132.3, 132.8, 113.9, 118.7, 119.4, 139.3, 140.2, 146.5, 146.6, 148.3, 148.6, 165.0, 166.1, 168.4, 169.7, 170.2, 171.3. MS (FAB) $m/z = 1175$ [M+Na]$^+$. HRMS (FAB) Calcd for $C_{72}H_{91}N_6O_7Na_2$ [M+Na$_2$]$^+$: 1197.6745. Found 1197.6788.
15. Spectral data of compound **4**: White amorphous. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (9H, br t), 1.16–1.38

(42H, br m), 1.54–1.70 (6H, br m), 3.89–3.99 (6H, br t), 7.04 (6H, br d, $J = 8.0$ Hz), 7.18 (6H, br d, $J = 8.0$ Hz), 7.46 (6H, br d, $J = 8.0$ Hz), 7.73 (6H, br d, $J = 8.0$ Hz), 8.07 (3H, br s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.7, 27.0, 27.9, 29.3, 29.3, 29.5, 29.5, 31.9, 50.1, 118.8, 127.7, 128.1, 129.8, 131.6, 131.8, 139.1, 147.5, 164.1, 169.9. MS (FAB) $m/z = 1135$ $[M+H]^+$. HRMS (FAB) Calcd for $C_{72}H_{91}N_6O_6$ $[M+H]^+$: 1135.7000. Found 1135.6979.

16. Spectral data of dimer of compound **4**: White amorphous. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (18H, br t), 1.24–1.67 (99H, m), 3.71 (3H, m), 3.93 (3H, m), 4.20 (3H, m), 5.60 (2H, d, $J = 8.8$ Hz), 6.32 (2H, d, $J = 8.8$ Hz), 6.81 (2H, d, $J = 8.4$ Hz), 7.06 (2H, d, $J = 9.2$ Hz), 7.14 (2H, d, $J = 8.8$ Hz), 7.22 (2H, d, $J = 8.4$ Hz), 7.29 (31H, m), 7.43 (2H, d, $J = 7.2$ Hz), 7.60 (2H, d, $J = 8.4$ Hz), 7.66 (2H, m), 8.06 (2H, d, $J = 8.4$ Hz), 8.11 (1H, br), 8.70–8.79 (2H, m). MS (ESI) $m/z = 2270$ $[M+H]^+$.