Hydrogen-Bonding-Induced Planar, Rigid, and Zigzag Oligoanthranilamides. Synthesis, Characterization, and Self-Assembly of a Metallocyclophane

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Hydrogen-Bonding-Induced Planar, Rigid, and Zigzag Oligoanthranilamides. Synthesis, Characterization, and Self-Assembly of a Metallocyclophane

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Four oligoanthranilamides **1**−**4**, which are incorporated with three, five, seven, or nine benzene units, respectively, have been synthesized and characterized. X-ray analysis, 1D and 2D ^{1}H NMR, and IR experiments reveal that all the new oligoamides adopt rigid, planar and zigzagged conformations in both solution and solid state, which are stabilized by intramolecular three-center hydrogen bonding. A 5-mer oligomer **22**, which is incorporated with two acetylene groups at the ends, has also been synthesized and utilized for the self-assembly of a rigid hydrogen-bonded metallocyclophane. The new rigid oligoanthranilamides represent useful building blocks for the construction of supramolecular architectures.

Introduction

Development of efficient methods to control the conformation or shape of complicated organic molecules is of importance both theoretically and for practical purpose. In particular, foldamers, the synthetic oligomers that are induced by noncovalent forces to fold into well-defined secondary structures, have received considerable interest in the past decade.[1] Among other noncovalent interactions such as metal−ligand coordination,[2] donor−acceptor interaction,[3] and solvophobic interaction,[4] hydrogen bonding has proven itself to be highly efficient for the formation of folding architectures. For example, Hamilton and Gong have utilized the three-center hydrogen-bonding motif to construct a number of structurally elegant aromatic oligoamide foldamers.[5,6] In principle, such efficient noncovalent approaches should also be useful for the formation of other kinds of unfolding conformations. Nevertheless, examples of such kinds of controllable artificial secondary structures are very limited.[7−9]

We recently initiated a project to develop simple components that could be connected iteratively to produce stable unfolding secondary structures. The long-term goal of the work is to create a new generation of functionalized

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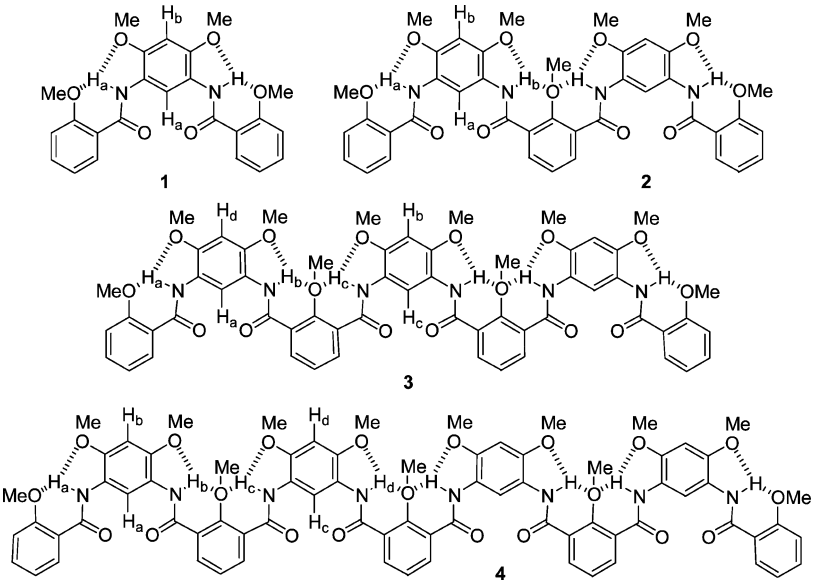
CHART 1



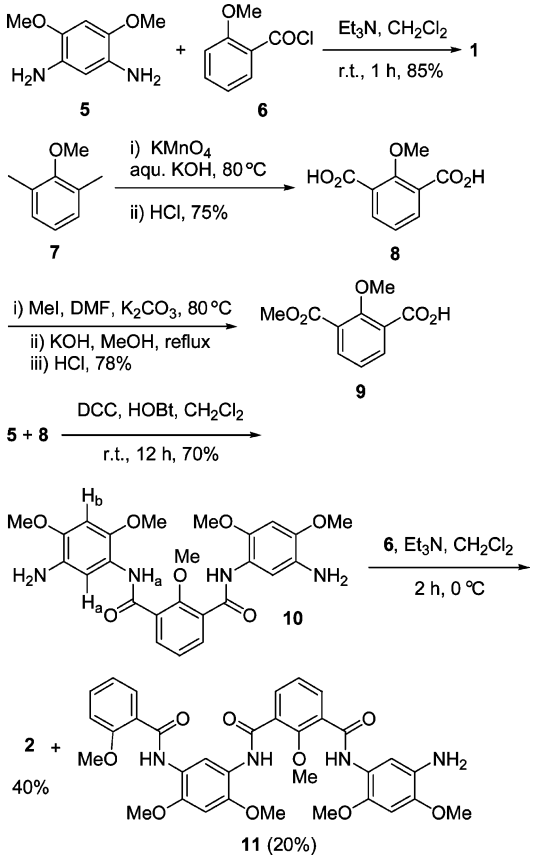
molecular and supramolecular scaffolds with new recognition or assembling properties. Previously, we have shown that readily available anthranilamide derivatives can be combined to form oligomers with linear, rigid, and planar secondary structures, which are stabilized by repeated three-center hydrogen bonding.[9,10] In this paper, we describe (1) a further development of this hydrogen-bonding approach for the formation of a new series of zigzagged oligoanthranilamide secondary structures and (2) the application of a rigid zigzagged anthranilamide diacetylene for the self-assembly of a new hydrogen-bonded metallocyclophane.[11,12]

Results and Discussion

Compounds **1**−**4**, which possess three, five, seven, or nine aromatic units, respectively, have been designed and synthesized (Chart 1). A previous study by Gong et al. had revealed that 2-methoxy-*N*-(2-methoxyphenyl)benzamide, the subunit for the present oligomers, takes up a rigid and planar structure due to the presence of two intramolecular hydrogen bonds.[5d] It was envisioned that the longer oligomers **1**−**4** should also adopt similar conformations with repeated zigzagged secondary structures.

The synthetic routes for 3-mer **1** and 5-mer **2** are presented in Scheme 1. Treatment of 1 equiv of diamine **5** with 2 equiv of acyl chloride **6** in dichloromethane with triethylamine as base afforded **1** in 85% yield. For the

SCHEME 1



synthesis of **2**, compound **7** was first oxidized to diacid **8** with potassium permanganate in hot potassium hydroxide solution. The latter was then converted into **9** by dimethylation, followed by a monohydrolysis reaction. Compound **5** was then coupled with 2 equiv of **8** in dichloromethane in the presence of DCC to produce trimer **10** in 70% yield. The reaction of diamine **10** with 1 equiv of **6** in dichloromethane and triethylamine afforded pentamer **2** and **11** in 40% and 20% yields,

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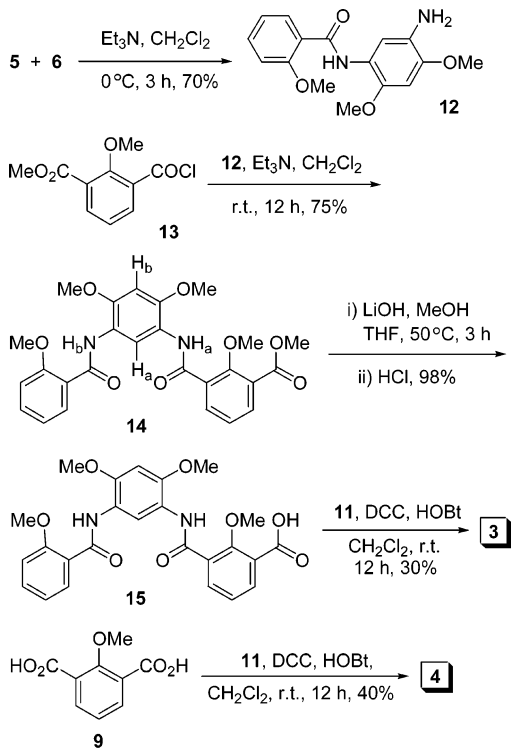
SCHEME 2



respectively. Under similar conditions, treatment of **10** with 2.2 equiv of **6** produced **2** in 85% yield.

For the synthesis of 7-mer **3**, compound **12** was first produced in 70% yield from the reaction of **5** and **6** in dichloromethane (Scheme 2). Under similar conditions, compound **12** reacted with **13** to afford **14** in 75% yield. The latter was then hydrolyzed with lithium hydroxide in hot THF and methanol to afford acid **15** quantitatively. Compound **15** was coupled with **11** in dichloromethane in the presence of DCC to produce 7-mer **3** in 30% yield. Under similar reaction conditions, 9-mer **4** was produced in 40% yield from the reaction of **9** and **11**. Similarly, treatment of diamine **5** with 2.2 equiv of **15** afforded **3** in 16% yield.

Single crystals of 3-mer **1** were grown by slow evaporation of the ethyl acetate solution at room temperature. Figure 1a shows the crystal structure of **1**. As expected, the NH bonds are involved in both five-membered (N−H···O distance = 2.23 Å) and six-membered (N−H···O distance = 1.83 Å) ring hydrogen bond, leading to a planar conformation. Evidence for the planar and zigzagged conformation of the oligoamides is provided by the X-ray structure of 5-mer **2**. The crystals of **2** were grown by slow evaporation of the chloroform solution at room temperature. As shown in Figure 1b, compound **2** possesses three sets of three-center hydrogen bonds. The N−H···O distances of the peripheral and central six-membered ring hydrogen bonds are 1.82 and 1.83 Å, respectively, while the N−H···O distances of the corresponding two five-membered ring hydrogen bonds are 2.22 and 2.24 Å, respectively. These values are very close to that revealed in the solid state of **1**, suggesting a similarity in the backbone of the compounds. In addition, all five benzene units and the amide groups in compound **2** also share one plane due to the presence of the strong intramolecular three-center hydrogen bonds. The backbone formed by the five benzene units also clearly displays a rigid zigzagged secondary structure. Since the longer 7-mer **3** and 9-mer **4** possess the identical structural subunit, it is reasonable to consider that these oligomers or even longer polymers of the same skeleton should also adopt similar planar and zigzagged conformations. A space filling model of planar 9-mer **4**, with a length of 4.60 nm, is shown in Figure 2, which reveals that the long oligomer takes up a slightly curved conformation due to the presence of the intramolecular hydrogen bonding. This result is consistent with the solid-state structure of 5-mer **2**, as shown in Figure 1b.

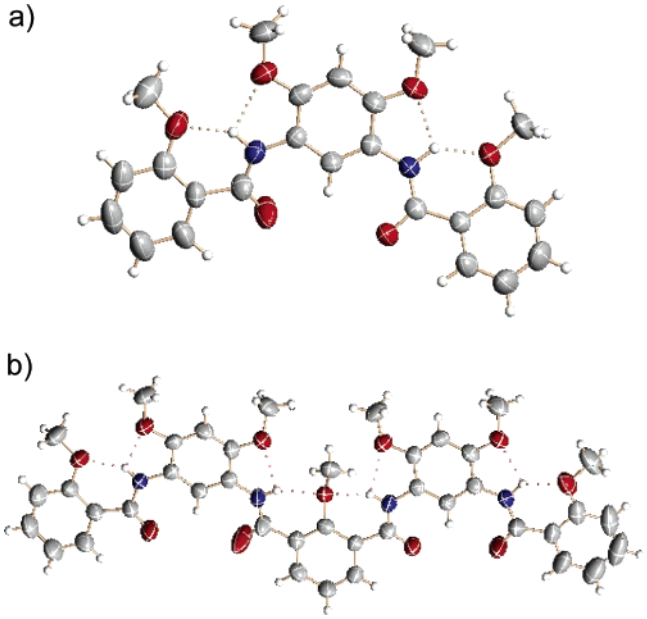


FIGURE 1. Crystal structures of 3-mer **1** (a) and 5-mer **2** (b). Both molecules adopt preorganized conformations due to the strong three-center hydrogen bonding.

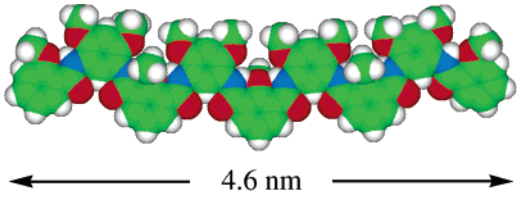


FIGURE 2. CPK model of 9-mer **4**, produced with AccuModel 2.1.

The solution conformations of the oligoamides were investigated by ^{1}H NMR in chloroform-*d*. The selected chemical shifts of oligomers **1**−**4** and intermediates **10** and **14** are collected in Table 1. The signals have been assigned based on the NOESY experiments. The ^{1}H NMR results show several features to support the rigid planar structures. In particular, large downfield shifts ($\Delta\delta$ 2.03−2.66 ppm) of the NH resonances were displayed for all the compounds, compared to that of 4-methoxy-*N*-(4-methoxyphenyl)benzamide (7.64 ppm).[5d] The H-2 resonances (PhH_a and PhH_c in Table 1) of the isophthalamide units of all the oligomers were also greatly downfield shifted due to the strong shielding effect of the two adjacent carbonyl groups, which are well consistent with the rigid planar conformation.[5e,6b] Adding 20% DMSO-d_6 to the solution of **1** in chloroform-*d* caused only a

TABLE 1. Selected ^{1}H NMR Resonances of Oligoanthranilamides (5.0 mM) in $CDCl_3$ at 25 °C

compd[a]	NH_a	NH_b	NH_c	NH_d	PhH	PhH_b	PhH_c	PhH_d
1	10.23				9.59	6.53		
1[b]	10.26				9.57	6.56		
2	10.30	9.74			9.56	6.54		
3	10.31	9.81	9.67		9.52	6.58	9.54	6.58
4	10.30	9.78	9.74	9.67	9.52	6.56	9.55	6.53
10	9.91				8.04	6.54		
14	10.29	10.11			9.58	6.58		

[a] The numbering is provided in the text. [b] In $CDCl_3$ with 20% of DMSO-d_6 (v/v).

relatively small chemical shift of the NH signal (<0.12 ppm), also indicating that the NH proton was involved in stable intramolecular hydrogen bonding.[5e,9] Further evidence for the role of the intramolecular hydrogen bonding in stabilizing the rigid zigzagged conformation of the oligomers comes from the temperature dependence of the NH resonance of **1** in chloroform-*d*, which reveals a small variation with temperature (1.8×10^{-3} ppm/K^{-1} from 0 to 55 °C), which is expected for intramolecularly hydrogen-bonded amide NH.[13] ^{1}H NMR NOESY experiments in chloroform-*d* revealed NOE connections between the NH protons and the neighboring methyl protons for all the oligomers investigated, which are also consistent with the proposed rigid conformation. ^{1}H NMR dilution experiments in chloroform-*d* revealed very small concentration dependence (<0.01 ppm in the range of 20−0.3 mM) for the NH and aromatic proton signals of **1** and **2**, showing that these rigid planar oligoamides have small aggregating tendency in chloroform. However, the existence of the three-centered hydrogen bonding in the molecules does not mean that the population of the hydrogen-bonded conformers is as high as 100% in the solution.

Compared to the signal of the periphery NH protons, the signals of the central NH protons of oligomers **2**−**4** move upfield significantly ($\Delta\delta_{max} = -0.64$ ppm for **3**). The result indicates that two NH units sharing the hydrogen bond donor (OMe) at the central area notably reduces the strength of the corresponding hydrogen bonding.

Infrared spectroscopy also supports the formation of intramolecular hydrogen bonding in stabilizing the rigid zigzagged conformation of the oligomers. The IR spectrum of **1**−**4** in chloroform displays N−H stretch peak at 3324, 3335, 3340, and 3336 cm^{-1}, respectively. Compound **14** shows two N−H stretching peaks at 3328 and 3298 cm^{-1}, respectively. All the stretching frequencies are those of typical hydrogen bonded N−H groups.[14] No peaks were displayed in the free N−H stretching region (3400−3500 cm^{-1}).[14] The NH stretching frequencies obtained in chloroform were also independent of the concentration changes within the concentration range of 25−2.0 mM, further indicating that these compounds adopt intramolecularly hydrogen-bonded rigid conformations.

The successful construction of the new class of rigid zigzagged secondary structures from readily available anthranilamide derivatives boded well for the development of new generation of rigid building blocks for supramolecular assemblies or recognition. To explore this possibility, compound **22** was prepared as the precursor for the preparation of a new rigid metallocyclophane.[15] The two acetylene groups in **22** were expected to be orientated on one side of the rigid backbone due to the presence of the intramolecular hydrogen bonding as established for 5-mer **2**, which would greatly facilitate the formation of the corresponding metallocyclophane. The syntheses of diacetylene **22** and metallocyclophane **23** are shown in Scheme 3. In brief, compound **16** was first reacted with iodine in methanol in the presence of silver sulfate to afford iodide **17** in 96% yield. The latter was then coupled with compound **18** in hot pyrrolidine with Pd(0) as catalyst to give compound **19** in 72% yield. Treatment of **19** with potassium hydroxide in hot methanol and then in hot benzene produced **21**, which was then coupled with diamine **10** in dichloromethane in the presence of DCC to afford **22** in 63% yield. Finally, **22** reacted with *trans*-$Pt(PEt_3)_2Cl_2$ in the presence of cupric chloride in dichloromethane to afford **23** in 18% yield.[16] Both **22** and **23** are soluble in common organic solvents such as chloroform and dichloromethane.

^{1}H NMR in chloroform-*d* revealed typical hydrogen-bonded NH resonances (**22**: 10.02 and 9.71 ppm; **23**: 9.99 and 9.72 ppm, respectively). Their NH and aromatic proton signals displayed very small concentration dependence (<0.01 ppm from 20 mM to 0.5 mM) and temperature dependence (2.5×10^{-3} and 2.6×10^{-3} ppm/K within the region of 0−55 °C). 2D-NOESY ^{1}H NMR studies revealed moderate strength of NOE connections between the NH and the neighboring OCH_3 and OCH_2 signals. All of these observations show that both the precursor and the metallocyclophane takes up a rigid and planar conformation as established for oligomers **1**−**4** as a result of the stable intramolecular hydrogen bonding.

Conclusion

In summary, we have reported a general efficient approach to constructing highly stable rigid, planar, and zigzagged secondary structures from anthranilamide derivatives by making use of intramolecular three-center hydrogen bonding. The work, to some extent, represents a conceptual derivation or extension from the very active foldamer chemistry to control the well-defined secondary structures of large synthetic molecules. Successful self-assembly of metallocyclophane **23** from rigid anthranilamide precursor **22** demonstrates the potential of the new rigid hydrogen bonded oligomers as building blocks for supramolecular self-assembly. Further work will focus on the modification of the skeleton to introduce additional

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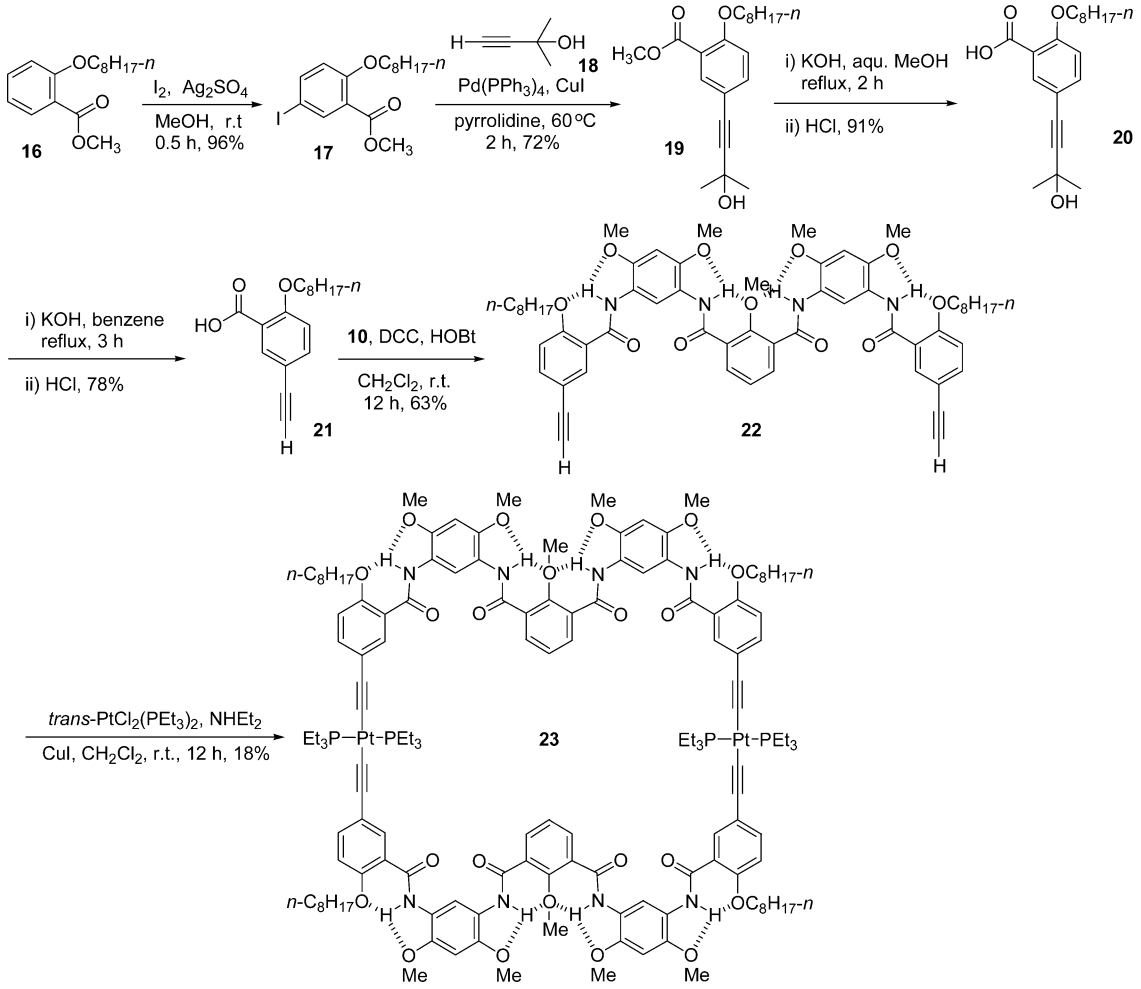
SCHEME 3



functional groups for assembling new giant supramolecular architectures, which will be reported in due course.

Experimental Section

Materials and Methods. Melting points are uncorrected. All reactions were performed under an atmosphere of dry nitrogen. The ^{1}H NMR spectra were recorded on a 400 MHz spectrometer, and chemical shifts are expressed in parts per million relative to the residual solvent protons as internal standards in an indicated solvent. Chloroform ($\delta = 7.26$ ppm) or TMS ($\delta = 0$ ppm) is used as an internal standard, respectively. Elemental analysis was carried out at the SIOC analytic center. Unless otherwise indicated, all starting materials were obtained from commercial suppliers and were used without further purifications. Solvents were purified according to standard procedures before use. Silica gel (10−40 μm) was used for all column chromatography.

***N,N′-m*-(4,6-Dimethoxy)phenylenebis(2-methoxy)benzamide (1).** To a stirred solution of compound **5**[17] (0.17 g, 1.00 mmol) and triethylamine (0.5 mL) in dichloromethane (20 mL) was added a solution of **6**[18] (0.30 g, 2.00 mmol) in dichloromethane (10 mL) dropwise in 0.5 h at room temperature. The mixture was stirred for 10 h at room temperature, washed with hydrochloric acid (1 N, 2 × 20 mL), water (20 mL), and brine (20 mL), and dried over sodium sulfate. After evaporation of the solvent under reduced pressure, the resulting residue was recrystallized from dichloromethane/petroleum ether (1:2) to afford compound **1** as colorless needles (0.38 g, 85%). Mp: 206−208 °C. ^{1}H NMR ($CDCl_3$): δ 3.94 (s, 6 H), 4.05 (s, 6 H), 6.57 (s, 1 H), 7.01 (d, $J = 7.8$ Hz, 2 H), 7.12 (t, $J = 7.8$ Hz, 2 H), 7.40 (m, 2 H), 8.36 (m, 2 H), 9.58 (s, 1 H), 10.25 (s, 2 H). ^{13}C NMR ($CDCl_3$): δ 56.0, 56.5, 95.6, 111.3, 115.1, 121.4, 121.5, 122.4, 132.6, 132.7, 145.6, 157.3, 162.4. IR ($CHCl_3$): ν 3324, 1653, 1618, 1600, 1553, 1535, 1484, 1467, 1430, 1342, 1295, 1234, 1201, 1097, 1037, 921, 748 cm^{-1}. MS (EI): *m*/*z* 436 $[M]^+$. Anal. Calcd for $C_{24}H_{24}N_2O_6$: C, 66.04; H, 5.54; N, 6.42. Found: C, 66.19; H, 5.57; N, 6.43.

2-Methoxyisophthalic Acid (8). A suspension of compound **7** (7.00 g, 50.0 mmol), potassium permanganate (52.0 g, 0.33 mol), and potassium hydroxide (9.00 g, 0.16 mol) in water (250 mL) was stirred at 80 °C for 3 h and then cooled to room temperature. The solid was filtered off, and the filtrate was acidified with concentrated hydrochloric acid to pH = 7. The resulting precipitate was filtered, washed with water, and dried in vacuo. After recrystallization from ethanol, the desired product was obtained as a white solid (7.30 g, 75%). M.p. 220−221 °C (219−221 °C[19]). ^{1}H NMR (DMSO-d_6): δ 3.80 (s, 3 H), 7.26 (t, $J = 7.5$ Hz, 1 H), 7.80 (d, $J = 7.5$ Hz, 2 H), 13.12 (s, 2 H). ^{13}C NMR ($CDCl_3$): δ 52.7, 64.5, 123.5, 124.7, 125.0, 137.0, 137.1, 159.4, 165.2, 165.6. MS (EI): *m*/*z* 197 $[M + H]^+$.

2-Methoxyisophthalic Acid Monomethyl Ester (9). To a stirred suspension of compound **8** (2.00 g, 10.0 mmol) and potassium carbonate (4.10 g, 30.0 mmol) in DMF (50 mL) was

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(18) Aitken, R. A.; Burns, G.; Morrison, J. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3937.
(19) Wagner, P. J.; Meador, M. A.; Park, B.-S. *J. Am. Chem. Soc.* **1990**, *112*, 5199.

added methyl iodide (2.00 mL, 30.0 mmol) at room temperature. The mixture was stirred at 80 °C overnight and then concentrated in vacuo. The resulting residue was triturated with dichloromethane (150 mL), and the organic phase was washed with water (50 mL) and brine (50 mL) and dried over sodium sulfate. After removal of the solvent, a yellow oily residue was obtained (2.24 g) that was dissolved in methanol (30 mL). To the solution was added potassium hydroxide (0.56 g, 10.0 mmol), and the mixture was heated under reflux for 3.5 h and then concentrated under reduced pressure. The resulting oily residue was dissolved in water (40 mL) and then acidified with concentrated hydrochloric acid to pH = ca. 3. The solution was then extracted with dichloromethane (3 × 50 mL). The combined organic phase was washed with water and brine and dried over sodium sulfate. After the solvent was removed under reduced pressure, the crude product was recrystallized from ethyl acetate to give **9** as a white solid (1.64 g, 78%). Mp: 154−156 °C. ^{1}H NMR ($CDCl_3$): δ 3.98 (s, 3 H), 4.06 (s, 3 H), 7.34 (m, 1 H), 8.10 (m, 1 H), 8.34 (m, 1 H). MS (EI): m/z 210 $[M]^+$.

***N*,*N*′-Bis(5-amino-2,4-dimethoxyphenyl)-2-methoxyisophthalamide (10).** To a stirred solution of compounds **5** (0.70 g, 4.20 mmol) and **8** (0.41 g, 2.10 mmol) in tetrahydrofuran (100 mL) were added DCC (0.95 g, 4.60 mmol) and HOBt (0.62 g, 4.60 mmol) at room temperature. The solution was stirred for 12 h, and then the solid was filtered off. After workup, the crude product was purified by column chromatography (CH_2Cl_2/MeOH 100:1) to afford compound **10** as a yellow solid (0.73 g, 70%). ^{1}H NMR ($CDCl_3$): δ 3.65 (s, 4 H), 3.88 (s, 6 H), 3.92 (s, 6 H), 4.00 (s, 3 H), 6.55 (s, 2 H), 7.41 (t, J = 7.5 Hz, 1 H), 8.09 (s, 2 H), 8.25 (d, J = 7.5 Hz, 2 H), 9.92 (s, 2 H). ^{13}C NMR ($CDCl_3$): δ 56.1, 56.9, 64.0, 97.1, 108.6, 121.5, 125.4, 128.2, 129.9, 134.9, 141.7, 143.6, 155.8, 162.1. MS (ESI): m/z 497 $[M + H]^+$. Anal. Calcd for $C_{25}H_{28}N_4O_7$: C, 60.48; H, 5.68; N, 11.28. Found: C, 60.47; H, 5.77; N, 11.09.

***N*,*N*′-Bis[2,4-dimethoxy-5-(2-methoxybenzoylamino)-phenyl]-2-methoxyisophthalamide (2) and *N*-(5-Amino-2,4-dimethoxyphenyl)-*N*′-[2,4-dimethoxy-5-(2-methoxybenzoylamino)phenyl]-2-methoxyisophthalamide (11).** A solution of **6** (0.24 g, 1.40 mmol) in dichloromethane (20 mL) was added to a solution of **10** (0.70 g, 1.40 mmol) and triethylamine (1 mL) in dichloromethane (20 mL) at 0 °C. The mixture was stirred at room temperature overnight and then concentrated in vacuo. After workup, the crude product was purified by column chromatography (EtOAc/CH_2Cl_2 1:1) to afford compounds **2** as a pale yellow solid (0.43 g, 40%) and compound **11** as a pale yellow solid (0.18 g, 20%). Compound **2**. Mp: >250 °C. ^{1}H NMR ($CDCl_3$): δ 3.90 (s, 6 H), 3.95 (s, 6 H), 4.00 (s, 3 H), 4.04 (s, 6 H), 6.49 (s, 2 H), 6.99 (d, J = 8.2 Hz, 2 H), 7.12 (t, J = 7.3 Hz, 2 H), 7.40−7.49 (m, 3 H), 8.33−8.38 (m, 4 H), 9.59 (s, 2 H), 9.75 (s, 2 H), 10.33 (s, 2 H). ^{13}C NMR ($CDCl_3$): δ 56.1, 56.3, 56.5, 64.2, 95.5, 111.4, 115.4, 120.6, 121.5, 121.6, 122.2, 125.4, 128.2, 132.7, 132.8, 135.3, 146.0, 146.1, 155.9, 157.3, 162.2, 162.6. IR ($CHCl_3$): ν 3335, 1615, 1599, 1542, 1459, 1233, 1199, 909, 753 cm^{-1}. MS (ESI): m/z 765 $[M + H]^+$. Anal. Calcd for $C_{41}H_{40}N_4O_{11}\cdot H_2O$: C, 62.94; H, 5.42; N, 7.16. Found: C, 62.78; H, 4.93; N, 6.91. Compound **11**: ^{1}H NMR ($CDCl_3$): δ 3.65 (s, 2 H), 3.88 (s, 3 H), 3.93 (s, 3 H), 3.96 (s, 3 H), 3.97 (s, 3 H), 4.03 (s, 3 H), 4.07 (s, 3 H), 6.55 (s, 1 H), 6.61 (s, 1 H), 7.03 (d, J = 7.8 Hz, 2 H), 7.10 (t, J = 7.8 Hz, 2 H), 7.41−7.51 (m, 2 H), 8.10 (s, 1 H), 8.25−8.39 (m, 3 H), 9.55 (s, 1 H), 9.68 (s, 1 H), 9.96 (s, 1 H), 10.32 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ 56.0, 56.1, 56.2, 56.5, 56.9, 64.1, 95.5, 97.1, 108.7, 111.4, 115.4, 120.5, 121.4, 121.5, 121.7, 122.3, 125.4, 128.0, 128.4,129.8, 132.6, 132.8, 134.8, 135.3, 141.8, 143.6, 145.9, 146.1, 155.8,157.3, 162.0, 162.1, 162.6. IR ($CHCl_3$): ν 3321, 1734, 1669, 1553 cm^{-1}. MS (ESI): m/z 630 $[M + H]^+$. Anal. Calcd for $C_{33}H_{34}N_4O_9$: C, 62.85; H, 5.43; N, 8.88. Found: C, 62.16; H, 5.74; N, 8.15.

***N*-(5-Amino-2,4-dimethoxyphenyl)-2-methoxybenzamide (12).** A solution of compounds **5** (1.68 g, 10.0 mmol), **6** (1.70 g, 10.0 mmol), and triethylamine (2 mL) in dichloromethane was stirred at 0 °C for 3 h. After workup, the crude product was purified by column chromatography (dichloromethane) to give **12** as a white solid (0.21 g, 70%). ^{1}H NMR ($CDCl_3$): δ 3.61 (s, 2 H), 3.85 (s, 3 H), 3.90 (s, 3 H), 4.06 (s, 3 H), 6.53 (s, 1 H), 7.01 (d, d, J_1 = 0.9 Hz, J_2 = 8.1 Hz, 1 H), 7.12 (d, t, J_1 = 0.9 Hz, J_2 = 8.1 Hz, 1 H), 7.45−7.51 (m, 1 H), 8.16 (s, 1 H), 8.29 (d, d, J_1 = 2.1 Hz, J_2 = 8.1 Hz, 1 H), 10.43 (s, 1 H). MS (ESI): m/z 303 $[M + H]^+$. ^{13}C NMR ($CDCl_3$): δ 56.0, 56.1, 57.3, 97.4, 108.6, 111.4, 121.4, 122.3, 122.4, 130.0, 132.3, 132.8, 141.6, 143.1, 157.3, 162.5. IR ($CHCl_3$): ν 3443, 3319, 1643, 1551 cm^{-1}. Anal. Calcd for $C_{16}H_{18}N_2O_4$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.56; H, 6.02; N, 9.19.

***N*-[2,4-Dimethoxy-5-(2-methoxybenzoylamino)phenyl]-2-methoxyisophthalamic Acid Methyl Ester (14).** This compound was prepared from **12** (0.91 g, 3.00 mmol) and **13**[20] (0.68 g, 3.00 mol) on the basis of the method described above for **1**. After workup, the crude product was purified by column chromatography (EtOAc/CH_2Cl_2 1:1) to afford **14** (1.11 g) in 75% yield as a pale yellow solid. ^{1}H NMR ($CDCl_3$): δ 3.94 (s, 3 H), 3.96 (s, 3 H), 3.97 (s, 3 H), 4.01 (s, 3 H), 4.06 (s, 3 H), 6.58 (s, 1 H), 7.02 (d, J = 8.4 Hz, 1 H), 7.12 (t, J = 7.8 Hz, 1 H), 7.32 (t, J = 7.8 Hz, 1 H), 7.44−7.47 (m, 1 H), 7.94−7.97 (m, 1 H), 8.35−8.38 (m, 1 H), 8.43−8.46 (m, 1 H), 9.58 (s, 1 H), 10.11 (s, 1 H), 10.30 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ 52.4, 56.0, 56.2, 56.5, 63.8, 95.4, 111.4, 115.2, 120.7, 121.5, 122.3, 124.5, 125.1, 128.6, 132.7, 134.6, 136.5, 145.8, 145.9, 157.3, 159.0, 161.7, 162.5, 166.0. IR ($CHCl_3$): ν 3328, 3298, 1722, 1673, 1659, 1551 cm^{-1}. MS (ESI): m/z 495 $[M + H]^+$. Anal. Calcd for $C_{26}H_{126}N_2O_8$: C, 63.15; H, 5.30; N, 5.67. Found: C, 62.77; H, 5.31; N, 5.56.

***N*-[2,4-Dimethoxy-5-(2-methoxybenzoylamino)phenyl]-2-methoxyisophthalamic Acid (15).** A suspension of **14** (0.20 g, 0.40 mmol) and lithium hydroxide hydrate (82 mg, 2.00 mmol) in a mixture of tetrahydrofuran (10 mL) and methanol (10 mL) was stirred at 50 °C for 3 h and then cooled to room temperature. Water (60 mL) and hydrochloric acid (10%) were added to pH = 6. The resulting precipitate was filtered, washed thoroughly with water, and dried to give **15** as a pale yellow solid (0.19 g, 98%). ^{1}H NMR ($CDCl_3$): δ 3.95 (s, 3 H), 3.97 (s, 3 H), 4.07 (s, 3 H), 4.09 (s, 3 H), 6.60 (s, 1 H), 7.03 (d, J = 8.4 Hz, 1 H), 7.13 (t, J = 7.5 Hz, 1 H), 7.41 (t, J = 8.1 Hz, 1 H), 7.43−7.51 (m, 1 H), 8.21−8.24 (m, 1 H), 8.35−8.39 (m, 2 H), 9.47 (s, 1 H), 9.56 (s, 1 H), 10.34 (s, 1 H). ^{13}C NMR (DMSO-d_6): δ 56.4, 56.5, 56.7, 63.3, 96.8, 112.6, 114.8, 119.3, 120.5, 121.2, 121.3, 124.4, 128.7, 131.2, 133.1, 133.4, 145.9, 146.8, 155.3, 157.1, 161.6, 162.6. IR ($CHCl_3$): ν 3310, 1714, 1663, 1553 cm^{-1}. MS (ESI): m/z 481 $[M + H]^+$.

***N*,*N*′-(4,6-Dimethoxy-*m*-phenylene)bis[2-methoxy-3-[2,4-dimethoxy-5-(2-methoxybenzoylamino)phenyl]aminocarbonyl]benzamide (3).** A solution of compounds **15** (0.13 g, 0.28 mmol), **11** (0.18 g, 0.28 mmol), DCC (70 mg, 0.34 mmol), and HOBt (46 mg, 0.34 mmol) in dichloromethane (40 mL) was stirred at room temperature for 12 h. The solid was filtered off, and the filtrate was concentrated under reduce pressure. The resulting residue was subjected to column chromatography (CH_2Cl_2/MeOH 1:100−1:20) to afford the desired product as a white solid (90 mg, 30%). Mp: >250 °C. ^{1}H NMR ($CDCl_3$): δ 3.95 (s, 6 H), 3.97 (s, 6 H), 3.98 (s, 6 H), 4.05 (s, 6 H), 4.07 (s, 6 H), 6.57 (s, 1 H), 6.58 (s, 2 H), 7.02 (d, J = 7.8 Hz, 2 H), 7.13 (t, J = 7.8 Hz, 2 H), 7.40−7.48 (m, 4 H), 8.31−8.38 (m, 6 H), 9.53 (s, 1 H), 9.55 (s, 2 H), 9.67 (s, 2 H), 9.81 (s, 2 H), 10.32 (s, 2 H). IR ($CHCl_3$): ν 3340, 1673, 1542, 1338, 1236, 1198, 1028, 753 cm^{-1}. HRMS (MALDI-tof): m/z 1093 $[M + H]^+$. HRMS (MALDI-tof): calcd for $C_{58}H_{57}N_6O_{16}$ 1093.3825 $[M + H]^+$, found 1093.3837.

***N*,*N*′-Bis[2,4-dimethoxy-5-[2-methoxy-3-[2,4-dimethoxy-5-(2-methoxybenzoylamino)benzoylamino]]phenyl]-2-methoxyisophthalamide (4).** This compound was prepared from **9** (50 mg, 0.25 mmol) and **11** (0.32 g, 0.5 mmol) on the

(20) Naito, T.; Kuroda, E.; Miyata, O.; Ninomiya, I. *Chem. Pharm. Bull.* **1991**, *39*, 2216.

basis of the method described for **3**. After workup, the crude product was purified by column chromatography ($CHCl_3$/MeOH 1:35) to afford **4** as a white solid (142 mg, 40%). Mp: >250 °C. ^{1}H NMR ($CDCl_3$): δ 3.94 (s, 6 H), 3.97 (s, 6 H), 3.98 (s, 12 H), 4.05 (s, 9 H), 4.08 (s, 6 H), 6.54 (s, 2 H), 6.56 (s, 2 H), 7.01 (d, J = 8.4 Hz, 2 H), 7.12 (t, J = 7.8 Hz, 2 H), 7.39−7.47 (m, 5 H), 8.30−8.37 (m, 8 H), 9.52 (s, 2 H), 9.55 (s, 2 H), 9.67 (s, 2 H), 9.75 (s, 2 H), 9.81 (s, 2 H), 10.32 (s, 2 H). MS (MALDI-tof): m/z 1443 $[M + Na]^+$. IR ($CHCl_3$): ν 3336, 1672, 1617, 1543, 1467, 1342, 1239, 1201, 1110, 1034 cm^{-1}. Anal. Calcd for $C_{75}H_{72}N_8O_{21}$: C, 63.37; H, 5.11; N, 7.88. Found: C, 63.28; H, 5.56; N, 7.38.

Methyl 5-Iodo-2-(*n*-octyloxy)benzoate (17). A mixture of compound **16**[21] (14.0 g, 53.0 mmol), iodine (14.0 g, 55.0 mmol), and silver sulfate (17.0 g, 55.0 mmol) in methanol (200 mL) was stirred at room temperature for 0.5 h and then concentrated in vacuo. The resulting residue was triturated with ethyl acetate (300 mL). The organic phase was washed with water (80 mL × 2) and brine (80 mL) and dried over sodium sulfate. After the solvent was distilled under reduced pressure, the resulting residue was subjected to flash chromatography (dichloromethane/petroleum ether 10:1) to give compound **17** as a pale yellow oil (19.9 g, 96%). ^{1}H NMR ($CDCl_3$): δ 0.85−0.90 (m, 3 H), 1.25−1.48 (m, 10 H), 1.76−1.83 (m, 2 H), 3.87 (s, 3 H), 3.98 (t, J = 6.4 Hz, 2 H), 6.72 (d, J = 6.6 Hz, 1 H), 7.68 (d, d, J_1 = 6.6 Hz, J_2 = 2.2 Hz, 1 H), 8.04 (d, J = 2.2 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ 14.2, 22.5, 26.0, 29.5, 29.6, 31.8, 51.8, 69.4, 85.8, 115.4, 115.6, 137.9, 141.6, 156.7, 167.0. MS (EI): m/z 390 $[M]^+$. Anal. Calcd for $C_{16}H_{23}IO_3$: C, 49.24; H, 5.94. Found: C, 49.11; H, 6.21.

Methyl 5-(3-Hydroxy-3-methylbut-1-ynyl)-2-(octyloxy)benzoate (19). A suspension of compounds **17** (4.00 g, 10.3 mmol), **18** (1.30 g, 15.0 mmol), $Pd(PPh_3)_4$ (0.38 g, 0.50 mmol, 5%), and cupric iodide (0.10 g, 0.50 mmol) in pyrrolidine (30 mL) was stirred at 60 °C for 2 h and then concentrated under reduced pressure. The resulting residue was triturated with ethyl acetate (150 mL), and the organic phase was washed with dilute hydrochloric acid (0.5 N, 50 mL), water (50 mL × 2), and brine (50 mL) and dried over sodium sulfate. After the solvent was distilled under reduced pressure, the crude product was subjected to flash chromatography (dichloromethane) to give compound **19** (2.58 g, 72%) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 0.86−0.90 (m, 3 H), 1.28−1.50 (m, 10 H), 1.60 (s, 6 H), 1.77−1.84 (m, 2 H), 3.87 (s, 3 H), 4.02 (t, J = 6.6 Hz, 2 H), 6.88 (d, J = 6.5 Hz, 1 H), 7.47 (d, d, J_1 = 6.5 Hz, J_2 = 2.2 Hz, 1 H), 7.85 (d, J = 2.2 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ 14.1, 22.9, 26.0, 29.1, 29.3, 29.8, 32.0, 32.3, 51.9, 65.2, 69.0, 80.6, 92.9, 113.6, 113.7, 114.1, 133.8, 137.6, 157.4, 166.2. MS (EI): m/z 346 $[M]^+$. Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.67; H, 8.88.

5-(3-Hydroxy-3-methylbut-1-ynyl)-2-(octyloxy)benzoic Acid (20). Compound **19** (2.00 g, 5.80 mmol) and potassium hydroxide (0.56 g, 10.0 mmol) were added to a mixture of methanol (50 mL) and water (20 mL). The mixture was stirred under reflux for 2 h and concentrated to about 20 mL. The solution was neutralized with dilute hydrochloric acid to pH = 6 and then extracted with dichloromethane (80 mL × 2). The combined organic phase was washed with water and brine and dried over sodium sulfate. Upon removal of the solvent under reduced pressure, the resulting brown residue was subjected to flash chromatography (CH_2Cl_2/EtOAc 10:1) to give the desired acid as a yellow oil (1.75 g, 91%). ^{1}H NMR ($CDCl_3$): δ 0.85−0.90 (m, 3 H), 1.25−1.49 (m, 10 H), 1.60 (s, 6 H), 1.88−1.93 (m, 2 H), 4.22−4.26 (t, J = 6.6 Hz, 2 H), 6.96 (d, J = 6.4 Hz, 1 H), 7.56 (d, d, J_1 = 6.4 Hz, J_2 = 2.3 Hz, 1H), 8.22 (d, J = 2.3 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ 14.2, 22.9, 26.2, 29.2, 29.7, 31.6, 32.0, 65.1, 67.3, 80.2, 93.6, 113.7, 114.0, 114.2, 134.1, 138.4, 158.0, 169.2. MS (EI): m/z 332 $[M]^+$. Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 72.27; H, 8.64.

(21) Zeng, H.; Miller, R. S.; Flowers, R. A.; Gong, B. *J. Am. Chem. Soc.* **2000**, *122*, 2635.

5-Ethynyl-2-(*n*-octyloxy)benzoic Acid (21). To a solution of compound **20** in benzene (80 mL) was added potassium hydroxide (0.56 g, 10.0 mmol). The mixture was refluxed for 3 h. After workup, the crude product was subjected to column chromatography (CH_2Cl_2) to afford compound **21** as a pale yellow solid (1.50 g, 78%). Mp: 63−64 °C. ^{1}H NMR ($CDCl_3$): δ 0.86−0.90 (m, 3 H), 1.25−1.48 (m, 10 H), 1.89−1.94 (m, 2 H), 3.06 (s, 1H), 4.26 (t, J = 6.5 Hz, 2 H), 6.99 (d, J = 6.6 Hz, 1 H), 7.64 (d, d, J_1 = 6.5 Hz, J_2 = 2.2 Hz, 1 H), 8.32 (d, J = 2.2 Hz, 1 H), 10.84 (br, 1 H). ^{13}C NMR ($CDCl_3$): δ 14.2, 22.7, 26.5, 29.7, 29.9, 32.0, 68.4, 79.7, 82.1, 113.4, 113.6, 114.1, 129.8, 158.0, 169.4. MS (EI): m/z 274 $[M]^+$. Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 72.30; H, 8.17.

***N*^{1},*N*^{3}-Bis(5-(5-ethynyl-2-(octyloxy)benzamido)-2,4-dimethoxyphenyl)-2-methoxyisophthalamide (22).** To a stirred solution of compound **21** (0.20 g, 0.40 mmol), DCC (0.21 g, 1.00 mmol), and HOBt (0.16 g, 1.00 mmol) in dichloromethane (20 mL) was added a solution of compound **10** (0.25 g, 0.90 mmol) in dichloromethane (5 mL) at room temperature. Stirring was continued for 12 h at room temperature, and the insoluble materials were filtered off. The filtrate was concentrated under reduced pressure, and the resulting residue was subjected to column chromatography (CH_2Cl_2/MeOH 20:1) to afford the desired product as a pale yellow solid (0.29 g, 73%). Mp: 176−178 °C. ^{1}H NMR ($CDCl_3$): δ 0.84−0.88 (m, 6 H), 1.22−1.49 (m, 20 H), 1.92−2.01 (m, 4 H), 3.03 (s, 2 H), 3.88 (s, 6 H), 3.96 (s, 6 H), 4.00 (s, 3 H), 4.18 (t, J = 7.2 Hz, 4 H), 6.49 (s, 2 H), 6.92 (d, J = 7.4 Hz, 2 H), 7.40 (t, J = 7.5 Hz, 1 H), 7.53 (d, d, J_1 = 6.6 Hz, J_2 = 2.1 Hz, 2 H), 8.32 (d, J = 7.8 Hz, 2 H), 8.51 (d, J = 2.1 Hz, 2 H), 9.54 (s, 2 H), 9.71 (s, 2 H), 10.02 (s, 2 H). ^{13}C NMR ($CDCl_3$): δ 14.2, 22.7, 32.0, 29.2, 29.5, 25.9, 29.6, 68.2, 114.2, 155.2, 118.2, 135.9, 114.5, 132.5, 164.7, 82.2, 79.4, 55.8, 55.9, 100.9, 149.8, 149.9, 116.8, 116.9, 115.8, 164.7, 118.4, 158.4, 131.6, 122.0, 56.2. IR ($CHCl_3$): ν 3328, 1670, 1547 cm^{-1}. MS (MALDI-tof): m/z 1009 $[M + H]^+$, 1031 $[M + Na]^+$, 1047 $[M + K]^+$. Anal. Calcd for $C_{59}H_{68}N_4O_{11}$: C, 70.22; H, 6.79; N, 5.55. Found: C, 70.07; H, 6.98; N, 5.34.

Metallocyclophane 23. A suspension of compound **22** (0.20 g, 0.20 mmol), *trans*-$PtCl_2(PEt_3)_2$ (0.10 g, 0.20 mmol), cupric acid (10 mg), and diethylamine (1.0 mL) in dichloromethane (200 mL) was stirred at room temperature for 12 h. The insoluble materials were filtered off, and the solution was washed with water (50 mL × 2) and brine (50 mL) and dried over sodium sulfate. After removal of solvent in vacuo, the crude product was purified with column chromatography (CH_2Cl_2/MeOH 40:1) to afford compound **23** as a light yellow solid (52 mg, 18%). Mp: >250 °C. ^{1}HNMR ($CDCl_3$): δ 0.85−0.88 (m, 12 H), 1.19−1.47 (m, 80 H), 1.91−1.96 (m, 8 H), 2.20−2.26 (m, 24 H), 3.90 (s, 12 H), 3.96 (s, 12 H), 4.04 (s, 6 H), 4.14 (t, J = 7.2 Hz, 8 H), 6.56 (s, 4 H), 6.85 (d, J = 7.8 Hz, 4 H), 7.35 (d, J = 7.4 Hz, 4 H), 7.41 (t, J = 6.6 Hz, 2 H), 8.27 (s, 4 H), 8.34 (d, J = 7.5 Hz, 4 H); 9.60 (s, 4 H), 9.78 (s, 4 H), 10.14 (s, 4 H). ^{13}C NMR ($CDCl_3$): δ 9.6, 15.2, 17.8, 17.9, 18.2, 24.0, 27.6, 30.1, 30.6, 30.9, 33.2, 55.1, 55.8, 56.5, 70.3, 96.2, 101.9, 113.7, 116.8, 118.2, 121.0, 122.9, 123.5, 131.7, 135.4, 137.9, 146.0, 149.7, 155.9, 158.2, 163.8, 164.3. MS (MALDI-tof): m/z 2877 $[M + H]^+$. Anal. Calcd for $C_{142}H_{192}N_8O_{22}P_4Pt_2$: C, 59.28; H, 6.73; N, 3.89. Found: C, 58.78; H, 6.41; N, 3.48.

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Supporting Information Available: X-ray crystallographic data for compounds **1** and **2** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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