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'Two-point'-bound supramolecular complexes from semi-rigidified dipyridine receptors and zinc porphyrins

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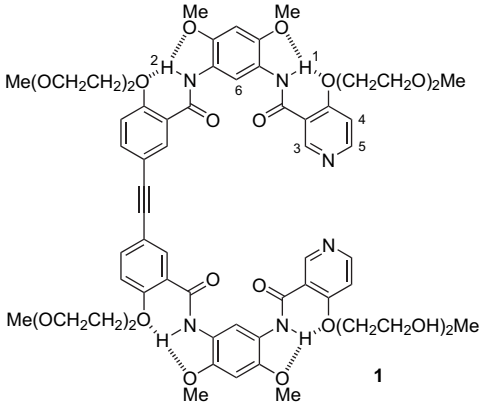
Abstract—Two linear compounds **1** and **2** have been designed and synthesized as new receptors for zinc porphyrins. Both compounds consist of two folded aromatic amide moieties, which are connected with an acetylene linker in **1** or directly in **2**. The rigid conformations of their folded moieties are stabilized by intramolecular tri-centered hydrogen bonding, while the whole molecule adopts a 'S'- or 'C'-styled conformation depending on the relative orientation of the two rigid moieties. Two pyridine units are introduced at the ends of **1** and **2** for the complexation of zinc porphyrin guests. Although the ^{1}H NMR investigation indicated that both compounds can bind two zinc porphyrin guests at high concentrations ($\geq$5 mM) in chloroform, the UV–vis studies revealed that, at low concentration of **1** and **2** (4 μM), both compounds complex one zinc porphyrin guest to form structurally unique 'two-point'-bound 1:1 complexes. The association constants of the 1:1 complexes have been determined with the UV–vis titration experiments.

1. Introduction

The coordination between zinc porphyrin–nitrogen ligand is one of the most used recognition motifs for supramolecular self-assembly.[1,2] Since metal-free and zinc porphyrins have strong absorption bands in the visible light region, their remarkable photoelectronic properties have been utilized to build various supramolecular molecular devices. The coordination bond between zinc porphyrin and nitrogen ligand exchanges rapidly and most supramolecular complexes assembled based on this coordination motif are also dynamic. It is well known that porphyrin zinc is pentacoordinated and therefore can bind only one nitrogen ligand.[3] Theoretically, for a symmetric zinc porphyrin, a nitrogen ligand can equally approach it from both sides of its skeleton macrocycle. However, the feature of pentacoordination implies that the central metal cannot simultaneously bind with two ligands. As a result, there always exists a dynamic equilibrium between the two processes.

Considering the great usefulness of the zinc porphyrin–nitrogen ligand binding motif in molecular recognition and supramolecular self-assembly, it would be of importance to develop suitable models to investigate this equilibrium.



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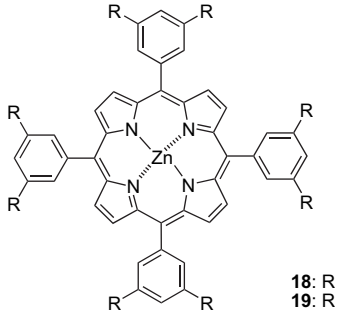
We recently reported the self-assembly of a new series of foldamers,[4] the folded or helical artificial secondary structures by making use of intramolecular hydrogen bonding as driving force.[5] The shape-persistent folded structures have been used as new generation of scaffolds for the construction of nonring synthetic receptors, which can efficiently recognize saccharides,[6] aliphatic ammonium,[7] and fullerenes.[8] In order to further explore the application of folded structures in molecular recognition, we had designed two hydrogen bonded semi-rigidified receptors **1** and **2**. In this paper, we report their synthesis and enhanced complexing properties to zinc porphyrins through an unique dynamic 'two-point' binding motif.

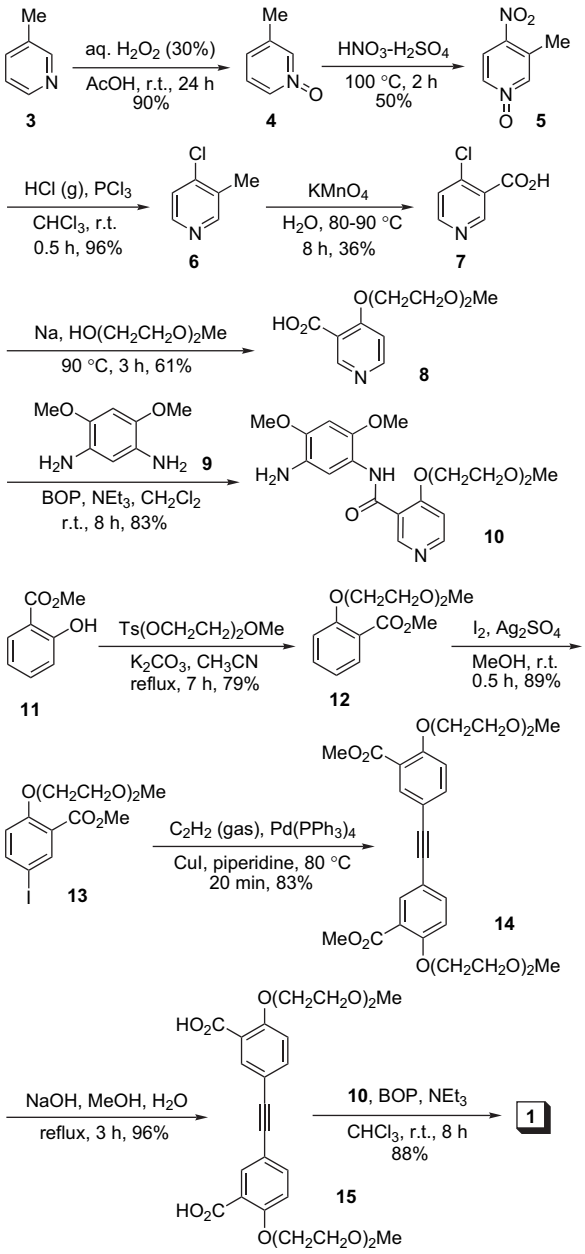
2. Results and discussion

The synthetic route of compound **1** is shown in Scheme 1. Thus, compound **7** was first prepared according to reported methods and then converted into **8** in 61% yield. The latter was coupled with **9** in dichloromethane in the presence of benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) to give **10** in 83% yield. Then, compound **12** was prepared by alkylation of **11** and followed by treatment with iodine in methanol to afford **13** in 89% yield. The Pd-catalyzed coupling reaction of **13** with acetylene in hot piperidine produced **14** in 83% yield. This diester was hydrolyzed to **15** and then coupled with **10** to give compound **1** in 88% yield.

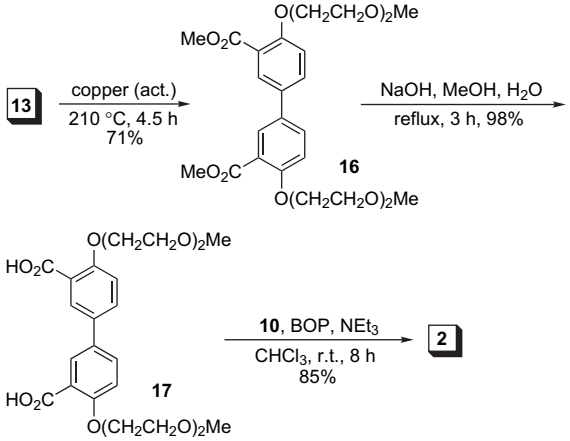
For the synthesis of compound **2** (Scheme 2), compound **16** was first obtained in 71% yield from the Ullman's coupling reaction of **13** and then hydrolyzed with sodium hydroxide to afford diacid **17** in 98% yield. The latter was coupled with **10** in chloroform in the presence of BOP to produce **2** in 85% yield.

The three-centered intramolecular hydrogen bonding motif in compounds **1** and **2** has been established by the X-ray analysis and the ^{1}H NMR and IR spectroscopy.[5b,8a,9] The ^{1}H NMR spectrum of **1** in chloroform-*d* is shown in Figure 1a. The aromatic signals of **1** have been assigned with the 2D NOESY and COSY techniques. It can be found that the two NH protons display two singlets (9.95 and 9.64 ppm, Fig. 1a) in the downfield area. The NH protons of **2** also appear in the downfield area (10.13 and 9.71 ppm, Fig. 1g). These results support that intramolecular hydrogen bonds are also present in both compounds. Due to the rotation of the acetylene unit in **1** and the biphenyl C–C bond in **2**, both compounds can in principle adopt a S- and C-styled conformations in solution. The fact that only one set of signals is observed in the ^{1}H NMR spectra suggests that the two conformations are in rapid exchange.





Scheme 1.



Scheme 2.

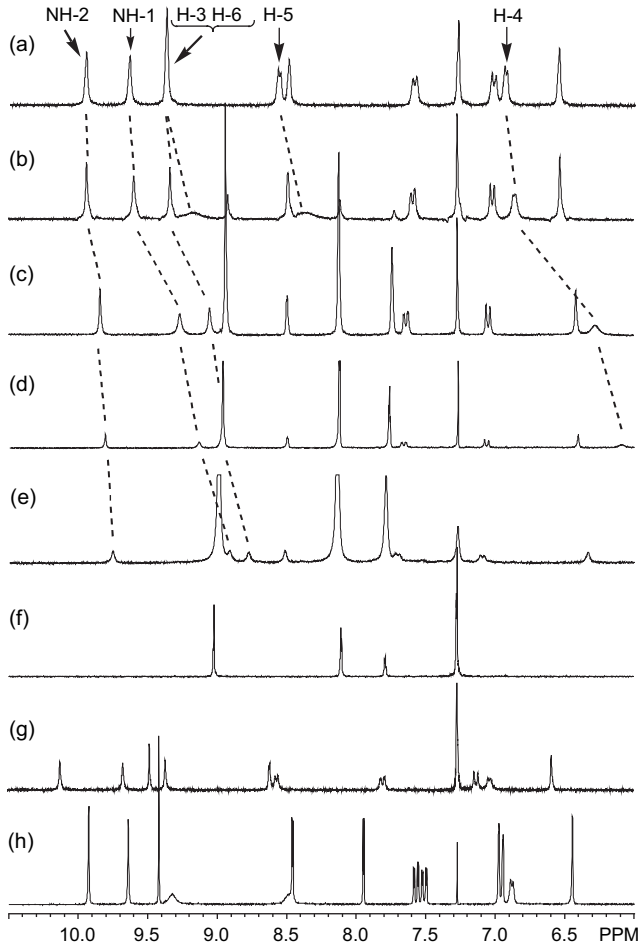


Figure 1. Partial ^{1}H NMR spectrum (400 MHz, 5 mM) of (a) **1**, (b) **1**+**18** (0.1 equiv), (c) **1**+**18** (1 equiv), (d) **1**+**18** (2 equiv), (e) **1**+**18** (4 equiv), (f) **18**, (g) **2**, and (h) **21** in chloroform-*d* at 25 °C.

Adding zinc porphyrin **18** to the solution of **1** in chloroform-*d* caused remarkable upfield shifting of the signals of several aromatic protons of **1** (Fig. 1b–e). For example, upon addition of 1 equiv of **18**, the NH-1 signal moved from 9.64 to 9.27 ppm, and the H-4 signal shifted from 6.93 to 6.28 ppm. In addition, obviously due to the complexation-induced shielding effect of **18**, the signals of H-3 and H-5 of **1** disappeared in the presence of **18** (Fig. 1c–e). Pronounced upfield shifting was also displayed for the pyrrole protons (−0.12 ppm) of **18** as a result of complexation with **1** (Fig. 1c,f). With the addition of more amount of **18**, the above signals of **1** further shifted upfield (Fig. 1d,e). This result may reflect continual approach to complexation saturation or the possibility that both pyridine units of **1** were bound to **18** to form a 1:2 complex. Similar results were also observed for the system of **2** and **18** in chloroform-*d*.

The complexation behavior of **1** and **2** with zinc porphyrin **18** and **19** in chloroform was then investigated by the UV–vis spectroscopy. As examples, the plots of the change of the UV–vis absorbance of **18** and **19** with the incremental addition of **1** are provided in Figures 2 and 3. Remarkable bathochromic effect was exhibited by both porphyrins, indicating strong intermolecular coordination. The Job's plot,

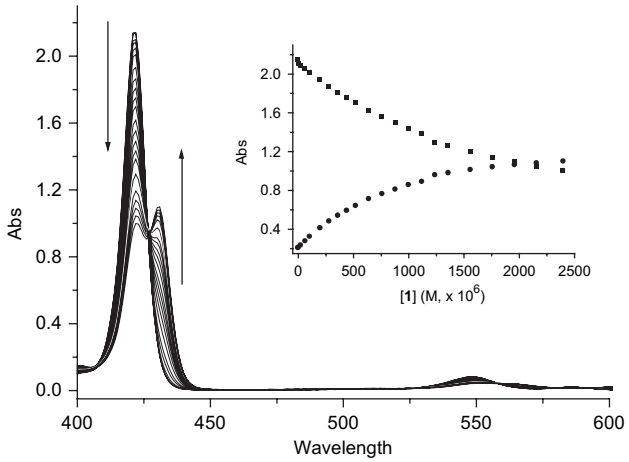


Figure 2. The change of the absorption spectra of **18** (4.0×10^{-6} M) with the addition of **1** (0–600 equiv) in chloroform at 25 °C (inset: plot of the absorption of **18** at 422 [■] and 431 [●] nm vs [**1**]).

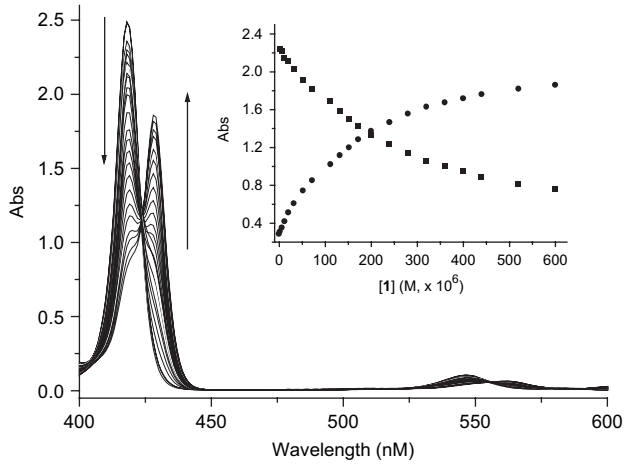


Figure 3. The change of the absorption spectra of **19** (4.0×10^{-6} M) with the addition of **1** (0–520 equiv) in chloroform at 25 °C (inset: plot of the absorption of **19** at 422 [■] and 431 [●] nm vs [**1**]).

based on the UV–vis experiments as shown in Figure 4 with the **1**:**18** system as an example, revealed maximum change in absorbance at [**1**]/([**1**]+[**18**])≈0.5, supporting a 1:1 stoichiometry.[10] In addition, all the UV–vis titration spectra display a clear isobestic point for the Soret band and the Q-band, also suggesting a 1:1 binding mode.[3a] It is obviously unreasonable to assume that only one pyridine unit of **1** or **2** was coordinated with the zinc porphyrin. Therefore, a 'two-point' binding motif should be formed for the complexes of such kind of shape-persistent two-pyridine derivatives with zinc porphyrin receptors. Figure 5 shows such kind of binding mode, with **1** as example of the two-pyridine molecules.

The association constant (K_a) of complexes **1**·**18**, **1**·**19**, **2**·**18**, and **2**·**19** was then evaluated by fitting their UV–vis titration data, obtained in chloroform, to a 1:1 binding mode,[8,11] which gave a value of 9.8 (±0.4)×10^2, 5.3 (±0.2)×10^3, 3.5 (±0.2)×10^2, and 2.8 (±0.1)×10^3 M^{-1}, respectively. Although in principle the coordinating ability of

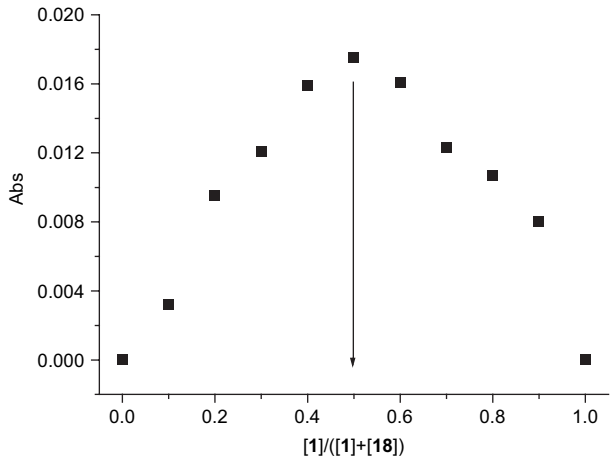


Figure 4. Job's plot of **1** versus **18**, revealing a maximum change of absorbance at 418 nm at **1**:**18**=0.5 ([**1**]+[**18**]=5×10^{-6} M in chloroform at 25 °C).

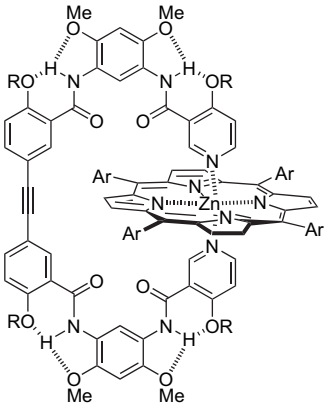
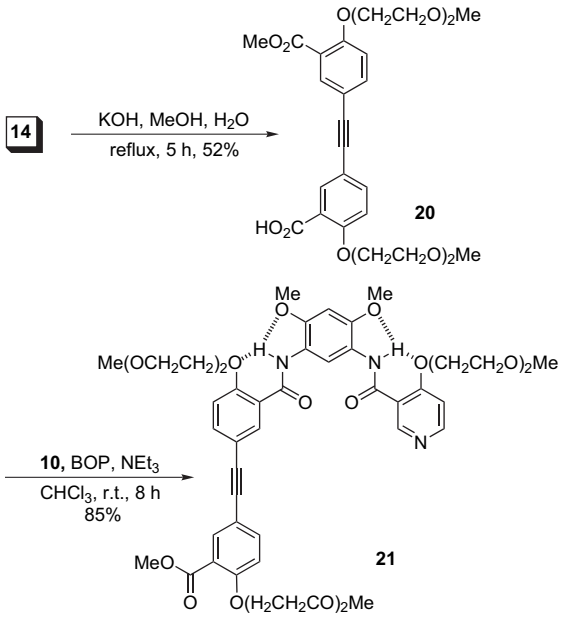


Figure 5. Proposed 'two-point' binding mode for the complex of **1** with a zinc porphyrin receptor.

octa-*tert*-butylated zinc porphyrin **18** is greater than **19** due to the electron-donating ability of the alkyl groups, the K_a of the complexes of **18** is pronouncedly smaller than the corresponding complexes of **19**. This result maybe rationalized by considering the increased steric hindrance of **18** relative to **19**, which reduces its binding affinity.

In order to detect whether this 'two-point' binding mode increases the stability of the corresponding complexes, compound **21** also was prepared (Scheme 3). Thus, compound **14** was first hydrolyzed with potassium hydroxide to give **20** in 52% yield. The acid was then reacted with **10** in chloroform with BOP as a coupling reagent to afford **21** in 85% yield. As expected, the ^{1}H NMR spectrum in chloroform-*d* showed two peaks for the NH protons in the downfield area (Fig. 1h), supporting the existence of intramolecular hydrogen bonding in **21**. On the basis of the UV–vis titration experiments, the K_a of complexes **18**·**21** and **19**·**21** in chloroform was determined to be 4.6 ($\pm$0.1)$\times10^2$ and 1.2 ($\pm$0.1)$\times10^3$ M^{-1}. These values are pronouncedly smaller than those of the corresponding complexes **1**·**18** and **1**·**19**. These results indicate that the existence of the second pyridine unit in **1** promotes the stability of the complexes.



Scheme 3.

Because the UV–vis experiments were performed at very low concentration of porphyrin receptors, the 1:1 binding mode revealed by the UV–vis investigations is not in conflict with the above ^{1}H NMR observation that both pyridine units of **1** and **2** may bind a zinc porphyrin to form a 1:2 complex. The concentration of the samples for the ^{1}H NMR experiments is obviously higher than that necessary for the UV–vis experiments. Therefore, a three-component complex maybe produced. At enough lowered concentration, the percentage of such three-component complexes maybe reduced to be ignorable and, as a result, only the formation of 1:1 complexes can be detected.

Because zinc porphyrin is of pentacoordination, the two-pyridine nitrogen atoms of **1** and **2** cannot bind with the porphyrin moiety simultaneously. Therefore, a dynamic equilibrium should exist for the 'two-point'-bonded 1:1 complexes as shown in Figure 6. Reducing the temperature of the 1:1 solution of **1** or **2** with **18** or **19** in chloroform-*d* to 0 °C caused important shifting of several aromatic signals of both components, but no splitting of the signals was observed. This result indicates that, within the studied temperature range, the exchange process shown in Figure 6 is quick on the ^{1}H NMR time scale. Further experiments at lowered temperature could not be performed due to the reduced solubility of **1** and **2**, therefore at the present stage we cannot determine the activation energy for this dynamic process.

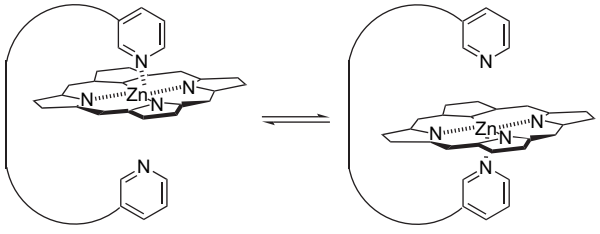


Figure 6. Dynamic process for the proposed 'two-point' binding mode for the complexes of **1** and **2** with zinc porphyrin guest.

3. Conclusion

In summary, we have reported the synthesis of a new series of semi-rigidified bipyridine receptors and their binding behavior toward zinc porphyrins. At high concentration, the new receptors can complex with two zinc porphyrin molecules to form 1:2 complexes, while at sufficiently lowered concentration, only 1:1 complexes are formed. Quantitative UV–vis experiments reveal that, for the 1:1 complexes, the existence of the second pyridine increases the stability of the complexes, which leads to the formation of an unique 'two-point' binding mode. Further work will focus on the design of more rigidified bipyridine receptors to quantitatively investigate the dynamic binding process of the 'two-point'-bound complexes.

4. Experimental

4.1. General methods

The ^{1}H NMR spectra were recorded on 400 or 300 MHz spectrometer in the indicated solvents. Chemical shifts are expressed in parts per million using residual solvent protons as internal standards. Chloroform (7.27 ppm) was used as an internal standard for chloroform-*d*. Elemental analysis was carried out at the SIOC Analytical Center. Unless otherwise indicated, all commercially available materials were used as received. All solvents were dried before use by following standard procedures. All reactions were carried out under an atmosphere of nitrogen. Silica gel (1–4 μ) was used for column chromatography. Compounds **4**,[12] **5**,[13] **6**,[14] **7**,[15] **9**,[16] **18**,[17] and **19**[18] were prepared according to reported methods. The methods for the determination of association constants have been reported in previous papers.[8]

4.1.1. 4-(2-(2-Methoxyethoxy)ethoxy)nicotinic acid (8). A suspension of sodium (0.84 g, 36.0 mmol) in 2-(2-methoxyethoxy)ethanol (10 mL) was stirred at 90 °C until a clear solution was formed. Compound **7** (1.40 g, 9.00 mmol) was then added in one portion. The reaction mixture was stirred at 90 °C for 3 h and then poured into ice water (50 mL). The solution was extracted with dichloromethane (20 mL×3). The aqueous phase was then concentrated under reduced pressure to about 10 mL and the resulting mixture was acidified with hydrochloric acid (5 N) to pH=3. The precipitate formed was filtered, washed with cold water, ether, dried in vacuo, and then recrystallized from ethanol to give compound **8** as a white solid (1.32 g, 61%). ^{1}H NMR (DMSO-d_6): 3.20 (s, 3H), 3.40–3.43 (m, 2H), 3.58–3.61 (m, 2H), 3.79 (t, *J*=4.8 Hz, 2H), 4.45 (t, *J*=4.8 Hz, 2H), 7.62 (d, *J*=6.0 Hz, 1H), 8.78 (d, *J*=6.0 Hz, 1H), 8.92 (s, 1H). ^{13}C NMR (DMSO): 57.99, 68.08, 69.86, 70.72, 71.19, 111.68, 119.65, 144.10, 145.60, 162.88, 168.51. MS (ESI): *m*/*z* 242 $[M+H]^+$. Anal. Calcd for $C_{11}H_{15}NO_5$: C, 54.77; H, 6.27; N, 5.81. Found: C, 54.35; H, 6.14; N, 5.88.

4.1.2. *N*-(5-Amino-2,4-dimethoxyphenyl)-4-(2-(2-methoxyethoxy)ethoxy)nicotinamide (10). To a solution of compound **8** (0.60 g, 2.48 mmol) and **9** (0.82 g, 4.48 mmol) in dichloromethane (50 mL) were added BOP (1.32 g, 2.98 mmol), DMAP (20 mg), and triethylamine (1 mL). The reaction mixture was stirred at room temperature for 8 h and diluted with dichloromethane (50 mL). The solution was washed with 10% aqueous Na_2CO_3 (30 mL×2), water (30 mL), brine (30 mL), and dried over sodium sulfate. Upon removal of the solvent in vacuo, the crude product was purified by column chromatography (CH_2Cl_2/MeOH 50:1) to afford compound **10** as a black powder (0.80 g, 83%). ^{1}H NMR ($CDCl_3$): 3.31 (s, 3H), 3.46–3.49 (m, 2H), 3.66–3.69 (m, 2H), 3.86 (s, 3H), 3.87 (s, 3H), 4.02 (t, *J*=4.5 Hz, 2H), 4.48 (t, *J*=4.5 Hz, 2H), 6.51 (s, 1H), 7.01 (d, *J*=6.0 Hz, 1H), 8.04 (s, 1H), 8.59 (d, *J*=6.0 Hz, 1H), 9.32 (s, 1H), 9.77 (s, 1H). ^{13}C NMR ($CDCl_3$): 56.05, 56.96, 59.00, 68.60, 68.87, 70.83, 71.91, 97.23, 107.56, 109.16, 118.38, 121.55, 129.78, 141.85, 143.62, 153.57, 154.11, 161.20, 162.30. IR (film): 3359, 2925, 1657, 1583, 1538, 1506, 1486, 1456, 1331, 1264, 1199, 1108, 1033 cm^{-1}. MS (EI): *m*/*z* 391 $[M]^+$. Anal. Calcd for $C_{19}H_{25}N_3O_6$: C, 58.30; H, 6.44; N, 10.74. Found: C, 58.42; H, 6.51; N, 10.51.

4.1.3. Methyl 2-(2-(2-methoxyethoxy)ethoxy)benzoate (12). A suspension of compound **11** (4.85 g, 30.0 mmol), anhydrous K_2CO_3 (4.97 g, 36.0 mmol), and 2-(2-methoxyethoxy)ethyl tosylate[3] (8.22 g, 30.0 mmol) in acetonitrile (100 mL) was stirred under reflux for 7 h and then cooled to room temperature. The solid was filtered off and the filtrate was concentrated under reduced pressure. The resulting residue was triturated with ethyl acetate (100 mL) and the solution was washed with hydrochloric acid (1 N, 30 mL×2), aqueous Na_2CO_3 solution (10%, 30 mL×2), brine (30 mL), and dried over sodium sulfate. Upon removal of the solvent in vacuo, the crude product was purified by column chromatography (petroleum ether/EtOAc 3:1) to afford compound **12** as colorless oil (6.00 g, 79%). ^{1}H NMR ($CDCl_3$): 3.39 (s, 3H), 3.55–3.59 (m, 2H), 3.76–3.80 (m, 2H), 4.37–4.41 (m, 5H), 4.22 (t, *J*=4.8 Hz, 2H), 6.96–7.02 (m, 2H), 7.42–7.45 (m, 1H), 7.79 (d, *J*=7.8 Hz, 1H). MS (EI): *m*/*z* 254 $[M]^+$. Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found C, 61.34; H, 7.08.

4.1.4. Methyl 5-iodo-2-(2-(2-methoxyethoxy)ethoxy)-benzoate (13). A suspension of compound **12** (5.90 g, 23.0 mmol), iodine (6.32 g, 25.0 mmol), and silver sulfate (6.98 g, 27.0 mmol) in dry methanol (100 mL) was stirred at room temperature for 0.5 h. After the solid was filtered off, the filtrate was evaporated in vacuo. The resulting residue was dissolved in dichloromethane (100 mL) and the solution was washed with saturated aqueous sodium bicarbonate solution (30 mL×2), water (30 mL), brine (30 mL), and dried over sodium sulfate. Upon removal of the solvent in vacuo, the crude product was purified by column chromatography (petroleum ether/EtOAc 3:1) to afford compound **13** as colorless oil (7.78 g, 89%). ^{1}H NMR ($CDCl_3$): 3.39 (s, 3H), 3.54–3.58 (m, 2H), 3.73–3.76 (m, 2H), 3.87–3.91 (m, 5H), 4.18 (t, *J*=4.8 Hz, 2H), 6.77 (d, *J*=9.0 Hz, 1H), 7.65 (dd, J_1=9.0 Hz, J_2=2.1 Hz, 1H), 8.05 (d, *J*=2.1 Hz, 1H). ^{13}C NMR ($CDCl_3$): 51.96, 58.86, 69.00, 69.31, 70.76, 71.82, 82.07, 115.96, 122.68, 139.79, 141.72, 158.07, 164.97. IR (film): 2953, 2923, 1728, 1607, 1487, 1434, 1281, 1225, 1081, 1063, 809, 783 cm^{-1}. MS (EI): *m*/*z* 380 $[M]^+$. Anal. Calcd for $C_{13}H_{17}IO_5$: C, 41.07; H, 4.51. Found: C, 41.57; H, 4.79.

4.1.5. Dimethyl 5,5′-(ethyne-1,2-diyl)bis(2-(2-(2-methoxyethoxy)ethoxy)benzoate) (14). A suspension of **13**

(1.14 g, 3 mmol), $Pd(PPh)_3$ (0.17 g, 0.15 mmol), and CuI (57 mg, 0.30 mmol) in dry piperidine (50 mL) was stirred at 35 °C. When the reaction mixture turned to orange from green, acetylene gas was introduced with a rubber balloon. The mixture was stirred under acetylene atmosphere at 80 °C for 0.2 h. The precipitate was filtered off and the filtrate was evaporated in vacuo. The resulting residue was triturated in ethyl acetate (50 mL) and the solution was washed with hydrochloric acid (1 N, 20 mL×2), water (30 mL), brine (30 mL), and dried over sodium sulfate. Upon removal of the solvent under reduced pressure, the crude product was purified by column chromatography (petroleum ether/EtOAc 2:1) to afford **14** as yellow oil (0.66 g, 83%). ^{1}H NMR ($CDCl_3$): 3.39 (s, 6H), 3.58–3.54 (m, 4H), 3.79–3.74 (m, 4H), 3.92–3.87 (m, 10H), 4.18 (t, J=4.8 Hz, 4H), 6.77 (d, J=9.0 Hz, 2H), 7.65 (dd, J_1=9.0 Hz, J_2=2.1 Hz, 2H), 8.05 (d, J=2.1 Hz, 2H). ^{13}C NMR ($CDCl_3$): 51.93, 58.92, 68.95, 69.41, 70.87, 71.92, 87.61, 113.64, 115.45, 120.77, 128.36, 128.46, 131.86, 131.95, 132.03, 134.86, 136.15, 158.08, 165.75. IR (film): 2926, 2878, 1732, 1610, 1504, 1451, 1437, 1277, 1244, 1145, 1110, 1081, 1053, 820 cm^{-1}. MS (EI): m/z 531 $[M]^+$. Anal. Calcd for $C_{28}H_{34}O_{10}$: C, 63.39; H, 6.46. Found: C, 63.43; H, 6.21.

4.1.6. 5,5′-(Ethyne-1,2-diyl)bis(2-(2-(2-methoxyethoxy)-ethoxy)benzoic acid) (15). To a solution of **14** (0.60 g, 1.10 mmol) in methanol (15 mL) and water (5 mL) was added sodium hydroxide (0.40 g, 10.0 mmol). The mixture was stirred under reflux for 4 h and then concentrated to about 5 mL. The residue was acidified with hydrochloric acid to pH=3 and the resulting precipitate was filtered, washed with cold water, ether, and dried in vacuo. The crude product was then recrystallized from ethanol to give compound **15** as a white solid (0.54 g, 97%). ^{1}H NMR (DMSO-d_6): 3.22 (s, 6H), 3.44–3.40 (m, 4H), 3.63–3.59 (m, 4H), 3.74 (t, J=4.8 Hz, 4H), 4.18 (t, J=4.8 Hz, 4H), 7.16 (d, J=9.0 Hz, 2H), 7.63 (dd, J_1=9.0 Hz, J_2=2.1 Hz, 2H), 7.74 (d, J=2.1 Hz, 2H). ^{13}C NMR (DMSO-d_6): 58.00, 68.59, 68.64, 69.83, 71.26, 87.58, 114.15, 122.25, 133.33, 135.48, 157.16, 166.36. MS (ESI): m/z 503 $[M+H]^+$. Anal. Calcd for $C_{26}H_{30}O_{10}$: C, 62.14; H, 6.02. Found: C, 62.38; H, 6.03.

4.1.7. *N*-(5-(5-((3-(2,4-Dimethoxy-5-(4-(2-(2-methoxy-ethoxy)ethoxy)nicotinamido)phenylcarbamoyl)-4-(2-(2-methoxyethoxy)ethoxy)phenyl)ethynyl)-2-(2-(2-methoxyethoxy)ethoxy)benzamido)-2,4-dimethoxyphenyl)-*N*-(2-(2-methoxyethoxy)ethoxy)nicotinamide (1). To a solution of **10** (212 mg, 0.54 mmol) and **15** (134 mg, 0.27 mmol) in dichloromethane (30 mL) were added BOP (0.26 g, 0.59 mmol), DMAP (20 mg), and triethylamine (0.1 mL). The mixture was stirred at room temperature for 6 h and then diluted with dichloromethane (50 mL). The solution was then washed with aqueous Na_2CO_3 solution (10%, 30 mL×2), water (30 mL), brine (30 mL), and dried over sodium sulfate. Upon removal of the solvent in vacuo, the crude product was purified by column chromatography (CH_2Cl_2/MeOH 30:1, then 10:1) to afford compound **1** as a pale yellow solid (0.29 g, 86%). ^{1}H NMR ($CDCl_3$): 3.29 (s, 12H), 3.43–3.47 (m, 8H), 3.67–3.71 (m, 8H), 3.94 (s, 12H), 4.00–4.03 (m, 8H), 4.41–4.50 (m, 8H), 6.53 (s, 2H), 7.00–7.02 (m, 4H), 7.58 (d, J=9.0 Hz, 2H), 8.47–8.50 (m, 4H), 9.32–9.37 (m, 4H), 9.64 (s, 2H), 9.95 (s, 2H). ^{13}C NMR ($CDCl_3$): 56.30, 59.03, 68.58, 68.91, 69.18, 70.76, 70.84, 71.96, 88.12, 95.67, 107.61, 113.26, 116.92, 120.45, 120.90, 122.94, 135.66, 135.98, 146.57, 146.83, 153.30, 154.23, 156.28, 161.17, 162.01, 162.43. MS (MALDI-TOF): m/z 1250 $[M]^+$, 1272 $[M+Na-H]^+$. HRMS (MALDI-TOF) Calcd for $C_{64}H_{77}N_6O_{20}$ $[M-H]^+$: 1249.5171. Found: 1249.5187.

4.1.8. Dimethyl 4,4′-bis(2-(2-methoxyethoxy)ethoxy)-biphenyl-3,3′-dicarboxylate (16). An intimate mixture of **13** (1.76 g, 4.60 mmol) and activated copper bronze[4] (3.50 g, 55.0 mmol) was covered with a thin layer of copper bronze and heated at 210–220 °C (internal temperature) for 4.5 h and then cooled to room temperature. The mixture was triturated with hot ethyl acetate (50 mL) and the organic phase was worked up. Upon removal of the solvent in vacuo, the crude product was purified by column chromatography (ethyl acetate) to afford **16** as colorless oil (0.83 g, 71%). ^{1}H NMR ($CDCl_3$): 3.40 (s, 6H), 3.57–3.60 (m, 4H), 3.77–3.80 (m, 4H), 3.91–3.95 (m, 10H), 4.26 (t, J=4.8 Hz, 4H), 7.05 (d, J=9.0 Hz, 2H), 7.64 (dd, J_1=9.0 Hz, J_2=2.1 Hz, 2H), 7.99 (d, J=2.1 Hz, 2H). ^{13}C NMR ($CDCl_3$): 51.93, 58.95, 69.12, 69.54, 70.86, 71.94, 114.27, 121.01, 129.66, 131.30, 132.20, 157.59, 166.57. IR (film): 2925, 2878, 1725, 1610, 1490, 1437, 1285, 1238, 1085, 1066, 1029, 924, 814, 786 cm^{-1}. MS (ESI): m/z 507 $[M+H]^+$. Anal. Calcd for $C_{26}H_{34}O_{10}$: C, 61.65; H, 6.77. Found: C, 61.64; H, 7.02.

4.1.9. 4,4′-Bis(2-(2-methoxyethoxy)ethoxy)biphenyl-3,3′-dicarboxylic acid (17). To a solution of **16** (0.70 g, 1.40 mmol) in methanol (20 mL) and water (5 ml) was added sodium hydroxide (0.40 g, 10 mmol). The mixture was stirred under reflux for 4 h and then concentrated to about 5 mL. The resulting residue was acidified with hydrochloric acid to pH=3 and then filtered. The solid was washed with cold water, ether, dried in vacuo, and then recrystallized from ethanol to give **17** as a white solid (0.66 g, 98%). ^{1}H NMR (DMSO-d_6): 3.22 (s, 6H), 3.33–3.44 (m, 4H), 3.59–3.75 (m, 4H), 3.75 (t, J=4.8 Hz, 4H), 4.18 (t, J=4.8 Hz, 4H), 7.16 (d, J=9.0 Hz, 2H), 7.63 (dd, J_1=9.0 Hz, J_2=2.1 Hz, 2H), 7.74 (d, J=2.1 Hz, 2H). ^{13}C NMR (DMSO-d_6): 58.00, 68.64, 68.73, 69.82, 71.26, 114.49, 122.19, 128.03, 130.43, 131.05, 156.51, 167.08. MS (MALDI-TOF): m/z 478 $[M]^+$. Anal. Calcd for $C_{24}H_{30}O_{10}$: C, 60.24; H, 6.32. Found: C, 60.12; H, 6.43.

4.1.10. N^3,$N^{3\prime}$-Bis(2,4-dimethoxy-5-(4-(2-(2-methoxy-ethoxy)ethoxy)nicotinamido)phenyl)-4,4′-bis(2-(2-methoxyethoxy)ethoxy)biphenyl-3,3′-dicarboxamide (2). To a solution of **10** (0.20 g, 0.51 mmol) and **17** (0.12 g, 0.25 mmol) in dichloromethane (30 mL) were added BOP (0.25 g, 0.55 mmol), DMAP (20 mg), and triethylamine (0.1 mL). The reaction mixture was stirred at room temperature for 6 h and then diluted with dichloromethane (50 mL). The solution was washed with aqueous Na_2CO_3 solution (10%, 30 mL×2), water (30 mL), brine (30 mL), and dried over sodium sulfate. Upon removal of the solvent in vacuo, the crude product was purified by column chromatography (CH_2Cl_2/MeOH 30:1, then 10:1) to afford **2** as pale yellow solid (0.26 g, 85%). ^{1}H NMR ($CDCl_3$): 3.28 (s, 6H), 3.30 (s, 6H), 3.46–3.52 (m, 8H), 3.69–3.73 (m, 8H), 3.96 (s, 6H), 3.99 (s, 6H), 4.02–4.07 (m, 8H), 4.46–4.53 (m, 8H),

6.58 (s, 2H), 7.03 (d, J=6.0 Hz, 2H), 7.13 (d, J=8.6 Hz, 2H), 7.80 (dd, J_1=8.6 Hz, J_2=2.4 Hz, 2H), 8.57 (d, J=6.0 Hz, 2H), 8.62 (d, J=2.4 Hz, 2H), 9.37 (s, 2H), 9.48 (s, 2H), 9.67 (s, 2H), 10.13 (s, 2H). ^{13}C NMR ($CDCl_3$): 56.33, 56.35, 59.04, 68.53, 68.91, 69.27, 70.74, 70.84, 71.95, 71.97, 95.79, 107.53, 109.01, 113.74, 116.71, 118.42, 120.56, 121.31, 122.93, 130.58, 130.96, 133.29, 141.64, 146.34, 146.70, 153.43, 154.42, 155.87, 161.20, 162.35, 162.75, 164.21. IR (film): 3358, 2885, 1661, 1615, 1583, 1549, 1484, 1470, 1424, 1337, 1308, 1277, 1243, 1222, 1202, 1109, 1030, 921, 813. MS (MALDI-TOF): m/z 1225 $[M+H]^+$, 1247 $[M+Na]^+$. HRMS (MALDI-TOF) Calcd for $C_{62}H_{77}N_6O_{20}$ $[M+H]^+$: 1225.5165. Found: 1225.5187.

4.1.11. 5-((3-(Methoxycarbonyl)-4-(2-(2-methoxyethoxy)-ethoxy)phenyl)ethynyl)-2-(2-(2-methoxyethoxy)ethoxy)-benzoic acid (20). To a solution of **14** (0.40 g, 0.76 mmol) in methanol (20 mL) was added potassium hydroxide (52 mg, 0.76 mmol). The reaction mixture was stirred at reflux for 6 h. After normal work up, the crude product was purified by column chromatography (CH_2Cl_2/MeOH 30:1) to afford **20** as colorless oil (0.22 g, 56%). ^{1}H NMR ($CDCl_3$): 3.31 (s, 3H), 3.32 (s, 3H), 3.49–3.53 (m, 4H), 3.64–3.71 (m, 4H), 3.82 (s, 3H), 3.82–3.87 (m, 4H), 4.17 (t, J=4.8 Hz, 2H), 4.33 (t, J=4.8 Hz, 2H), 6.89–6.96 (m, 2H), 7.49–7.59 (m, 2H), 7.89 (s, 1H), 8.23 (s, 1H). ^{13}C NMR ($CDCl_3$): 52.10, 59.07, 59.12, 68.63, 69.01, 69.33, 69.50, 70.78, 70.97, 71.88, 72.00, 87.06, 88.59, 113.64, 113.69, 115.18, 117.86, 120.79, 136.08, 136.39, 136.82, 137.32, 156.94, 158.35. IR (film): 2926, 2880, 1732, 1610, 1503, 1453, 1416, 1275, 1244, 1109, 1083, 1047, 917, 821. MS (ESI): m/z 517 $[M+H]^+$. Anal. Calcd for $C_{27}H_{32}O_{10}$: C, 62.78; H, 6.24. Found: C, 62.64; H, 6.02.

4.1.12. Methyl 5-((3-(2,4-dimethoxy-5-(4-(2-(2-methoxy-ethoxy)ethoxy)nicotinamido)phenylcarbamoyl)-4-(2-(2-methoxyethoxy)ethoxy)phenyl)ethynyl)-2-(2-(2-methoxy-ethoxy)ethoxy)benzoate (21). To a solution of **10** (74 mg, 0.19 mmol) and **20** (0.10 g, 0.19 mmol) in dichloromethane (30 mL) were added BOP (0.10 g, 0.23 mmol), DMAP (20 mg), and triethylamine (0.1 mL). The reaction mixture was stirred at room temperature for 6 h and then diluted with dichloromethane (50 mL). The solution was washed with aqueous Na_2CO_3 solution (10%, 30 mL×2), water (30 mL), brine (30 mL), and dried over sodium sulfate. Upon removal of the solvent in vacuo, the crude product was purified by column chromatography (CH_2Cl_2/MeOH 30:1) to afford **21** as pale yellow solid (136 mg, 80%). ^{1}H NMR ($CDCl_3$): 3.27 (s, 6H), 3.37 (s, 3H), 3.42–3.47 (m, 4H), 3.54–3.57 (m, 2H), 3.63–3.68 (m, 4H), 3.73–3.76 (m, 2H), 3.87–3.92 (m, 8H), 3.94–4.00 (m, 4H), 4.22 (t, J= 4.8 Hz, 2H), 4.35–4.42 (m, 4H), 6.44 (s, 1H), 6.88 (d, J=6.0 Hz, 2H), 6.94–6.98 (m, 2H), 7.51 (dd, J_1=8.6 Hz, J_2=2.4 Hz, 1H), 7.57 (dd, J_1=8.6 Hz, J_2=2.4 Hz, 2H), 7.95 (d, J=2.4 Hz, 1H), 8.43–8.54 (m, 2H), 9.33 (br, 1H), 9.42 (s, 1H), 9.64 (s, 1H), 9.92 (s, 1H). ^{13}C NMR ($CDCl_3$): 52.03, 56.30, 59.03, 68.68, 68.88, 69.02, 69.15, 69.50, 70.75, 70.82, 70.96, 71.93, 72.01, 87.80, 88.02, 95.65, 113.17, 113.72, 115.69, 116.82, 116.94, 120.43, 120.77, 122.94, 134.98, 135.44, 136.16, 136.37, 146.55, 146.88, 156.29, 158.14, 161.03, 162.00, 165.84. IR (film): 3359, 2884, 1732, 1666, 1614, 1584, 1544, 1503, 1468, 1272, 1242, 1202, 1108, 1086, 1030, 918, 821 cm^{-1}. MS (MALDI-TOF): m/z 912 $[M+Na]^+$. HRMS (MALDI-TOF) Calcd for $C_{46}H_{55}N_3O_{15}Na$ $[M+Na]^+$: 912.3553. Found: 912.3525.

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