

Self-assembly of indolocarbazole-containing macrocyclic molecules†

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A successful approach for the synthesis of indolocarbazole-containing macrocycles based upon π - π stacking preorganization of indolocarbazole planes and click-chemistry reactions has been developed. The macrocycles are able to form folded structures with the help of hydrogen-bonding and π - π stacking interactions. Two of the receptors were successfully characterized by single-crystal X-ray diffraction analysis. Our results confirmed that they showed different interesting self-assembly with the anions due to the N-H...X⁻ and the triazole C-H...X⁻ hydrogen-bonding.

Introduction

Molecular receptors designed to bind anionic guests is an attracting area of research.¹ Many recognized anion receptors have been widely employed such as amides,² pyrrole,³ indole,^{4,5,6} urea,^{7,8} guanidiniums⁹ and so on. Among them, the indolocarbazole-based anion receptors attracted much more attention due to the strong anion binding ability and emerged as an important anion-binding agents reported by Beer and co-workers.⁴ Inclusion of indolocarbazole-containing macrocyclic derivatives was described by the Jeong and co-workers.^{5,10} Moreover, Flood and co-workers found that 1,2,3-triazoles had strong C-H...X⁻ contacts very recently.¹¹ Strategies in the synthesis of anion receptors including high dilution techniques,¹² supramolecular templated techniques,¹³ were demonstrated and the shape diversity of the receptors were generated, such as linear-like,⁸ tripod-like,¹⁴ shape-persistent macrocycles,^{5,10} capsule¹⁵ and cryptand.¹⁶ Understanding the structure–function relationships that relate specifically to receptors could lead to new “design rules” for producing benign, high-performance receptors substances. We envisioned the construction of larger structures to increase the size and complexity of the substrates within the molecular recognition event. As the model shown in Fig. 1, we proposed the structure of the new receptors in which two planes could form folded structure. The cavity formed can self-assemble some anions by the H-donating groups. Here, we developed the synthesis of indolocarbazole-containing macrocycles benefiting from π - π stacking preorganization of indolocarbazole plane. The plane was coupled with resorcin through flexible chain by “click chemistry”, four novel molecular receptors with different numbers of indolocarbazoles were synthesized.

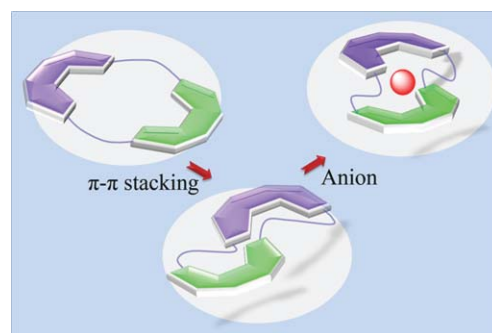


Fig. 1 Schematic of the π - π stacking interactions in macrocycle 2 and the interaction with the anion.

Results and discussion

Macrocycles 1, 2, 3 and 4 were obtained with the yield for the final click step of 90% for 1, 40% for 4, 15% for 2 and < 5% for 3 respectively (Scheme 1). Compound 5 was synthesized in accordance with Jeong's literature procedures.⁵ It was observed that macrocycle 1 was obtained in a yield of 90% and < 5% of macrocycle 2 was formed in a highly dilute concentration. However, high-concentration benefits to obtain macrocycle 2, the yield of macrocycle 2 increased to about 15% and a new macrocycle 3 appeared in a yield of < 5% in high-concentration, meanwhile the yield of macrocycle 1 reduced to about 20%. This is due to easy formation of π - π aggregation between indolocarbazole planes. On the contrary, < 5% of macrocycle 2 was formed in a highly dilute concentration, because the interaction of π - π aggregation is weak.

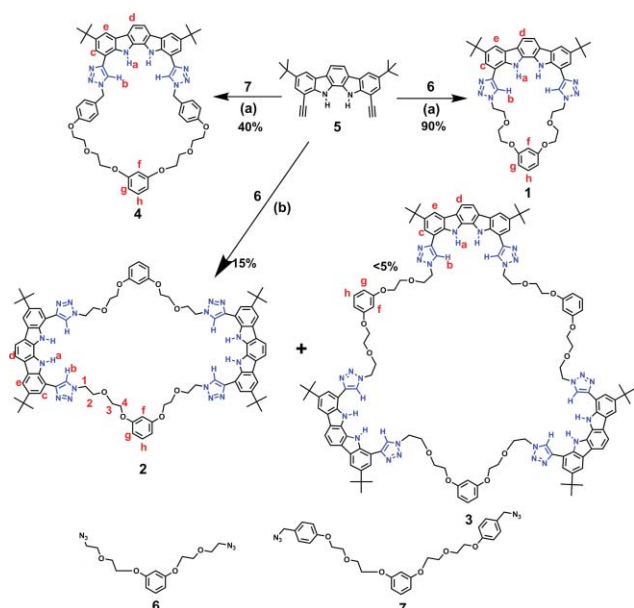
The structural features of the macrocycles 1 and 2 were confirmed by single-crystal X-ray diffraction analysis (Fig. 2). Macrocycles 1 and 2 can form a folded structure attributing to the π - π interaction between the indolocarbazole and the resorcin ring in macrocycle 1 or between the indolocarbazoles in macrocycle 2. The macrocycle 1 contains an internal cavity surrounded by hydrogen atoms in N-H group and other two hydrogen atoms in triazole C-H group. The distance between the indolocarbazole plane and the resorcin ring is about 3.1 Å. The two nitrogen atoms which closed to the indolocarbazoles in two triazoles were turned to the same direction, one of the nitrogen atoms can interact by hydrogen-bonding with one N-H (H_a) and the other can interact with the outside H_c. The distance between the two

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Scheme 1 Reaction conditions: a) CuI, DBU, toluene, pseudo high-dilution condition, dropwise, 70 °C, 5 h, 90% for **1** and 70 °C, 24 h, 40% for **4**; b) CuI, DBU, toluene, concentrated solution, 70 °C, 24 h, 15% yields for **2** and <5% for **3**.

triazoles is 6.7 Å, the length is enough to support a linear C–H...Cl interaction.¹⁷ In the macrocycle **2**, the intramolecular π – π interaction is between the two indolocarbazoles (the distance between the two indolocarbazole plane is 3.5 Å.). The nitrogen atoms in triazoles turn to the internal cavity resulting in hydrogen bonding interaction between the two N–H (H_a) and the nitrogen atoms in triazoles. The semicircular defined a space-filling cavity with a diameter of about 6.0 Å.

The properties of macrocycles **1**, **2** and **4** in solution were studied by ¹H NMR spectroscopy (Fig. 3). In macrocycle **4**, two benzene rings were introduced to prohibit the π – π stacking of the two planes, the H atoms in resorcin ring of macrocycle **4** (H_b , H_f and H_g) and compounds **6**, **7** show the same chemical shift. However, in macrocycle **1**, the resorcin ring can fold leading to π – π stack with the indolocarbazole plane, the H_b and H_g significantly shifted upfield about 0.5 and 0.34 ppm respectively. The results indicate macrocycle **1** in solution can maintain the conformation similar to that in the solid phase (the X-ray crystal structures analysis). Compared to **1**, the N–H (H_a) signals of **2** were significantly shifted downfield (1.1 ppm) indicating a stronger hydrogen bonding interaction between the H_a and the nitrogen atoms in triazoles. The H_c shifted upfield about 0.8 ppm, which could be attributed to the weakened hydrogen bonding interaction between the H_c and the nitrogen atoms in triazoles because the triazole-N turned to the internal cavity and formed hydrogen bond with the N–H (H_a). The 2D ¹H NMR NOESY of macrocycle **2** in D₂-tetrachloroethane at 0 °C showed the correlation between the indolocarbazole and the chain which indicated the folded conformation of the macrocycle **2** (see ESI, Fig. S1†). For the resorcin ring protons, compared to macrocycle **1**, the H_b , H_f and H_g shifted upfield much more (0.75, 0.55 and 0.75 ppm respectively), that could attribute to the shield effect of the indolocarbazole planes, which is sliding relative to each other in the solution (ESI, Fig. S2†). The upfield shift of

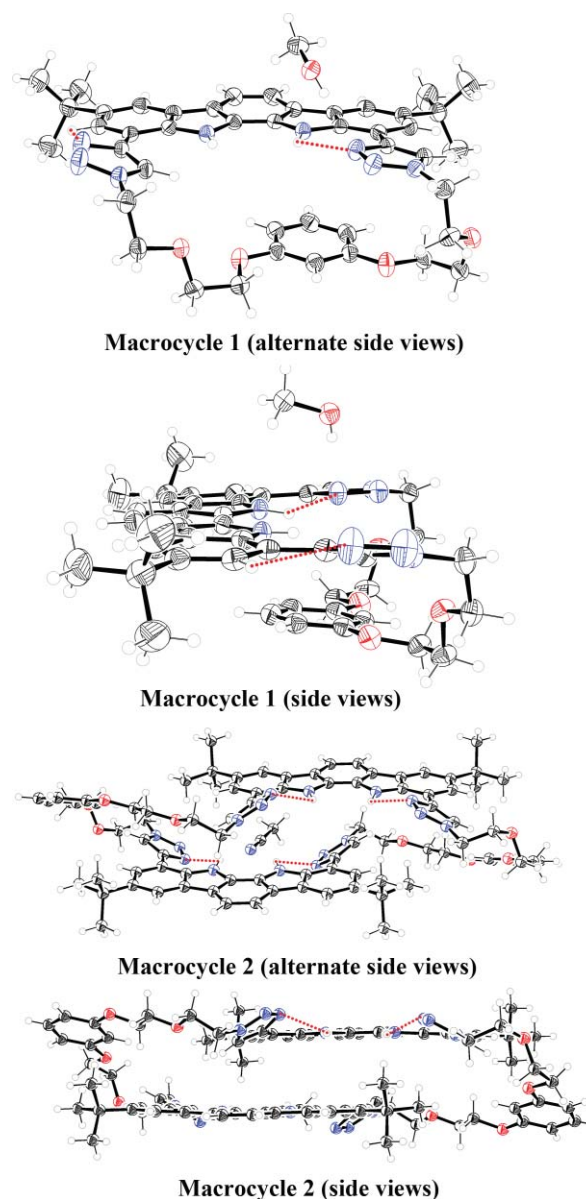


Fig. 2 Crystal structures of the macrocycles **1** and **2** (dotted line showed the hydrogen-bond interaction).

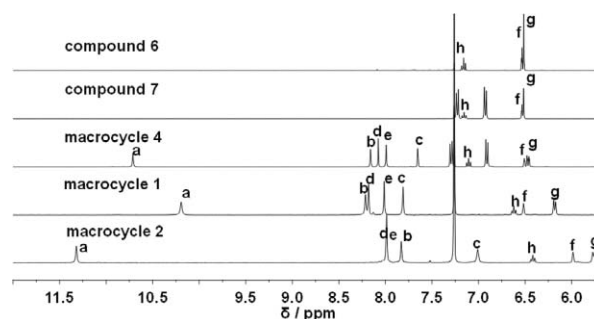


Fig. 3 Aromatic region of the ¹H NMR spectra (400 MHz, CDCl₃) of macrocycles **1**, **2**, **4**, compounds **6**, **7**.

protons H_d and H_e further supported the π – π aggregation of the two indolocarbazole planes.

The absorption and fluorescence spectra also showed the π - π interaction (Fig. S5†). The absorption of **2** showed a 3.5 nm red shift in comparison to **1**. The fluorescence spectra also showed the red shift and a remarkable increase at about 419 nm compared to the macrocycle **1**. Cl-responsive changes in the UV correlated with π - π stacking was confirmed (Fig. 4). With the increase of the Cl⁻, absorption of **2** showed a 4 nm blue shift which indicated that the π - π stacking between the two indolocarbazoles was weakened by the Cl⁻. The data of ¹H NMR combined with the UV and FL spectra supported the folded structure of the macrocycle **2** in solution.

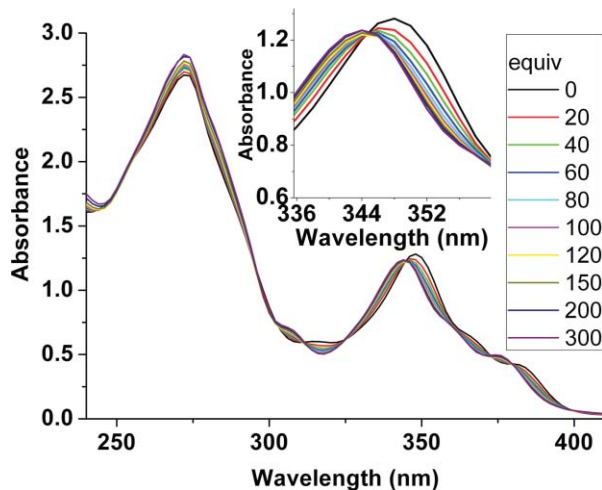


Fig. 4 UV spectral changes during titration of macrocycle **2** (1.0×10^{-5} M) with *n*-Bu₄NCl at 298 K in a CH₂Cl₂ solution.

The spherical anions F⁻, Cl⁻, Br⁻ and I⁻ were confirmed for binding to macrocycles **1** and **2** using ¹H NMR and UV titrations. *Ab initio* modeling (HF/3-21G) of the complexes formed between macrocycles **1**, **2** and the halides (Fig. 5) revealed two different binding modes. The volume of the anion affected the interaction with the N-H (H_a). In macrocycle **1**, both the Cl⁻ and Br⁻ ions can lie in the cavity which was formed from indole N-H (H_a) and the twisted triazole C-H (H_b). The small F⁻ ion is close to the side of indole N-H (H_a), and the I⁻ anion size is bigger, can only be outside of the cavity and interact with the triazole C-H (H_b). For macrocycle **2**, the four anions are all in the center of the cavity formed by the two indole ring plane. According to these data, two different binding mode with the receptors is expected.

The association constants (*K*_a) were determined by nonlinear fitting analyses of the ¹H NMR titration curves (Table 1). Job's plots (UV, Fig. S4†) showed that **1** and **2** formed 1 : 1 complexes with all the chosen anions. For the macrocycle **1**, the association constants for the four anions are in the order of F⁻ > Cl⁻ > Br⁻ > I⁻. This is probably attributed to the charge density of the anion surfaces and to the size complementarities of the anions and the internal cavity, which is in line with the molecular modeling results. For the macrocycle **2**, the association constants are much smaller than the macrocycle **1** with an order of F⁻ > Cl⁻ > Br⁻ > I⁻. The smaller binding affinity of macrocycle **2** with halides may arise from the greater rigidity of **1**.

The binding properties of **1** and **2** in solution were studied by ¹H NMR (Fig. S3†). With the addition of anions, the H_a and H_b signals of macrocycle **1** were significantly shifted downfield suggesting the formation of hydrogen bonds between

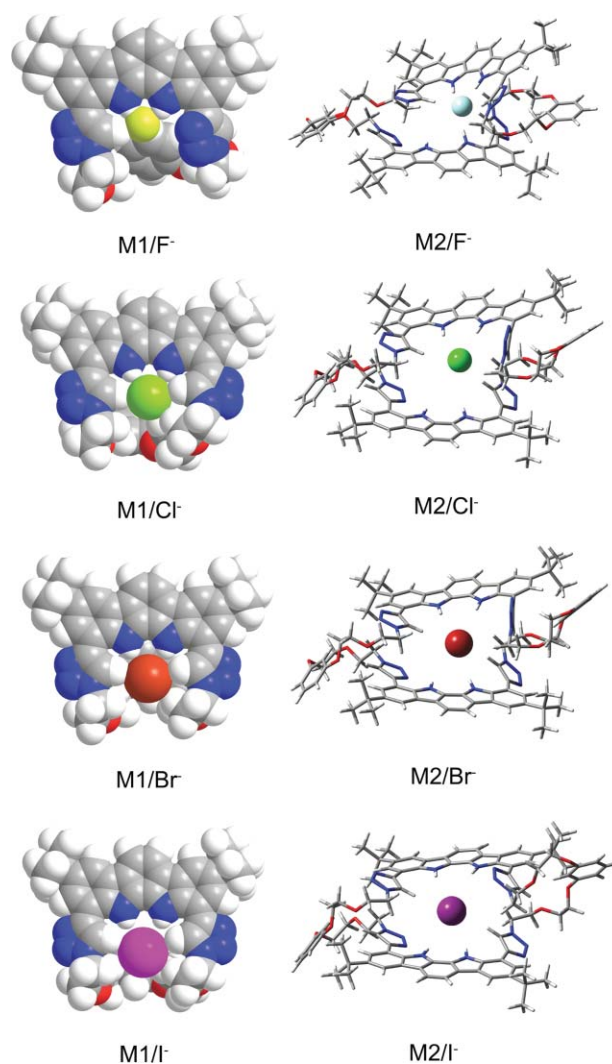


Fig. 5 Models (HF/3-21G) of the structures for halide complexation with macrocycles **1** and **2**.

Table 1 Association constants (*K*_a, M⁻¹) and triazole-H chemical shifts of complexes (CDCl₃) formed between **1**, **2** and anions

Anion	Chemical shift (δ , ppm)		Association constant (<i>K</i> _a , M ⁻¹)	
	1	2	1	2
F ⁻	9.01	9.10	11600	3010
Cl ⁻	9.55	9.81	1500	120
Br ⁻	9.44	9.25	325	16
I ⁻	8.88	7.85	106	4

(The errors in the *K*_a values were within 10%.)

the macrocycle **1** and the anions. With the increase of the halides' size, the triazole C-H (H_b) shifted to a greater extent than the N-H (H_a) protons. The downfield shift of the H_c indicates the increasing hydrogen bonding interaction between the H_c and the nitrogen atoms in the triazole when the triazole C-H (H_b) turned to the internal cavity to bind with the halides. The decreasing π - π interaction between the indolocarbazole and the resorcin ring

plane by addition of anions resulted in the hydrogen signals of the resorcin ring plane significantly shifted downfield.

In macrocycle **2**, the F^- ion is small and can penetrate into the cavity to interact with the H_a leading to H_a shifted downfield largely (2.2 ppm). H_b shifted downfield 1.2 ppm. In the case of Cl^- anion, H_a shifted downfield slightly (0.36 ppm), while H_b shifted downfield 1.5 ppm. For Br^- anion, H_a shifted upfield 0.15 ppm due to the combination effects of the broken of the hydrogen bonding between the H_a and the triazoles-N and the failure of the construction of $N-H(H_a) \cdots Br^-$ bonding. But the H_b shifted upfield significantly (1.2 ppm). The titration with the I^- anion showed little changes in the 1H NMR. The results indicates that the anions of F^- , Cl^- and Br^- were able to enter into the cavity. F^- and Cl^- can interact with $N-H(H_a)$ and the triazole protons (H_b). Br^- can only interact with H_b . The I^- is too large to enter into the cavity showing a little change in the 1H -NMR. This indicates a different mode of self-assembly compared to that of macrocycle **1**.

Conclusion

In summary, we have demonstrated a successful approach for the synthesis of indolocarbazole-containing macrocycles based upon π - π stacking preorganization of indolocarbazole planes and “click-chemistry” reactions. Our results confirm that two different self-assembly mode between the macrocycles **1**, **2** and the anions. Especially the interesting folded structures was achieved by macrocycle **2** and the anions leading to a new creation. Further investigations on highly response binding with other anions such as tetrahedral or trigonal anions by weak interaction tuning are under way.

Experimental

Synthesis of Macrocycles **1**, **2**, **3** and **4**

Macrocycle 1. 1,8-Diaza [5.4.0] bicycloundec-7-ene (DBU) (4.0 mmol, 0.7 mL) was added to toluene (200 mL), degassed (argon) for 30 min and heated to 70 °C while flushing with argon. At 70 °C, CuI (0.02 mmol, 3.8 mg) was added to the mixture. A solution of the **5** (208 mg, 0.5 mmol) and **6** (168 mg, 0.5 mmol) in THF (5 mL) and toluene (30 mL) was added to the solution slowly over 4 h and stirred for another 1 h under argon. The mixture was concentrated in vacuo. The product was purified *via* chromatography (SiO_2 , CH_2Cl_2 : Ethyl acetate : methanol 20:20:1) to afford **1** (330 mg, 90% yield) as a yellow solid. 1H NMR (400 MHz, $CDCl_3$) δ 10.19 (s, 2H), 8.21 (s, 2H), 8.18 (s, 2H), 8.01 (s, 2H), 7.81 (s, 2H), 6.62 (t, J = 8.0 Hz, 1H), 6.52 (s, 1H), 6.18 (d, J = 8.1 Hz, 2H), 4.70 (s, 4H), 4.13 (s, 8H), 3.83 (s, 4H), 1.52 (s, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 146.6, 142.5, 134.5, 129.9, 126.4, 125.4, 121.4, 121.1, 119.9, 116.1, 113.1, 112.0, 107.7, 101.9, 69.5, 69.3, 68.0, 50.6, 34.8, 32.2. MALDI-TOF (M), Calcd for $C_{44}H_{48}N_8O_4$ (M) 752.38; Found 752.5.†

† Crystallographic data for Macrocycle **1**: $C_{45}H_{52}N_8O_5$, M_r = 784.95, monoclinic, space group = $P2_1/c$, a = 15.612(3), b = 13.356(3), c = 20.763(4) Å, β = 102.05(3), T = 173 K, Z = 4, μ = 0.082 mm⁻¹, $R_F(R_{wF})$ = 0.0649(0.1380) for 28188 observed independent reflections. Crystallographic data for Macrocycle **2**: $C_{46}H_{51}N_9O_4$, M_r = 793.96, monoclinic, space group = $P2_1/c$, a = 21.048(4), b = 11.504(2), c = 17.527(4) Å, β = 102.01(3), T = 173 K, Z = 4, μ = 0.084 mm⁻¹, $R_F(R_{wF})$ = 0.0646(0.1309) for 28221 observed independent reflections

Macrocycle 2. 1,8-Diaza [5.4.0] bicycloundec-7-ene (DBU) (4.0 mmol, 0.7 mL), **5** (416 mg, 1.0 mmol) and **6** (336 mg, 1.0 mmol) was added to THF (3 mL) and toluene (50 mL), degassed (argon) for 30 min and heated to 70 °C while flushing with argon. At 70 °C, CuI (0.02 mmol, 3.8 mg) was added to the mixture. A mixture solution was heated at 70 °C for over 20 h under argon. The mixture was concentrated in vacuo. The product was purified *via* chromatography (SiO_2 , CH_2Cl_2 : Ethyl acetate : methanol 20:20:1) to afford **2** (110 mg, 15% yield) as a yellow solid. 1H NMR (400 MHz, $CDCl_3$) δ 11.32 (s, 4H), 7.99 (s, 8H), 7.83 (s, 4H), 7.01 (s, 4H), 6.41 (t, J = 7.7 Hz, 2H), 5.98 (s, 2H), 5.76 (d, J = 8.0 Hz, 4H), 4.85 (s, 8H), 4.46 (s, 8H), 4.06 (s, 16H), 1.33 (s, 36H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 147.0, 141.7, 134.4, 129.2, 126.6, 125.2, 121.9, 121.4, 119.3, 116.97, 112.7, 111.9, 107.8, 100.7, 70.6, 70.1, 67.2, 51.0, 34.7, 32.2. MALDI-TOF, Calcd for $C_{88}H_{96}N_{16}O_8$ Na (M+Na)⁺ 1527.75; Found 1527.3 (M+Na)⁺.‡

Macrocycle 3. 1H NMR (600 MHz, $CDCl_3$) δ 11.08 (s, 6H), 8.03 (s, 6H), 7.98 (s, 6H), 7.85 (s, 6H), 7.21 (s, 6H), 6.53 (s, 3H), 5.93 (s, 9H), 4.61 (s, 12H), 4.12 (s, 12H), 3.78 (d, 24H), 1.37 (s, 54H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.2, 147.0, 141.7, 134.3, 129.2, 126.2, 125.0, 121.2, 121.2, 119.1, 115.7, 112.9, 111.7, 107.1, 100.8, 70.0, 69.6, 66.8, 50.5, 34.5, 32.0. MALDI-TOF, Calcd for $C_{132}H_{144}N_{24}O_{12}$ Na (M+Na)⁺ 2280.13; Found 2279.3. HRMS (ESI) Calcd for $C_{132}H_{145}N_{24}O_{12}$ (M+H)⁺ 2258.14683; Found 2258.16672 (M+H)⁺.

Macrocycle 4. 1,8-Diaza [5.4.0] bicycloundec-7-ene (DBU) (4.0 mmol, 0.7 mL) was added to toluene (200 mL), degassed (argon) for 30 min and heated to 70 °C while flushing with argon. At 70 °C, CuI (0.02 mmol, 3.8 mg) was added to the mixture. A solution of the **5** (208 mg, 0.5 mmol) and **7** (274 mg, 0.5 mmol) in THF (5 mL) and toluene (30 mL) was added to the solution slowly over 20 h and stirred for another 4 h under argon. The mixture was concentrated in vacuo. The product was purified *via* chromatography (SiO_2 , CH_2Cl_2 : Ethyl acetate : petroleum ether : methanol 5:5:10:1) to afford **4** (190 mg, 40% yield). 1H NMR (400 MHz, $CDCl_3$) δ 10.71 (s, 2H), 8.16 (s, 2H), 8.08 (s, 2H), 7.99 (s, 2H), 7.65 (s, 2H), 7.29 (d, J = 8.6 Hz, 4H), 7.11 (t, J = 8.2 Hz, 1H), 6.91 (d, J = 8.7 Hz, 4H), 6.51 (s, 1H), 6.47 (d, J = 8.2 Hz, 2H), 5.60 (s, 4H), 4.17 – 4.03 (m, 8H), 3.86 (m, 8H), 1.50 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 159.0, 148.2, 142.3, 134.9, 129.8, 129.1, 127.6, 126.4, 125.3, 121.3, 119.5, 119.1, 116.3, 115.2, 112.7, 112.0, 107.0, 102.2, 69.8, 69.7, 67.6, 67.5, 53.9, 34.8, 32.1. MALDI-TOF (M), Calcd for $C_{58}H_{60}N_8O_6$ (M) 964.46; Found 964.8. HRMS (ESI) Calcd for $C_{58}H_{61}N_8O_6$ (M+H)⁺ 965.47141; Found 965.46902 (M+H)⁺.

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