Macrocycles

Nanofabrication: Reversible Self-Assembly of an Imbedded Hexameric Metallomacrocycle within a Macromolecular Superstructure**

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Molecular imprinting[1] processes widely occur in complex biosystems, thus, selective and specific guests bound by antibodies, such as hormones, are vital for basic cell–cell communication. Experimental simulation of cell imprinting[2,3] has been predominately developed by using bulk polymerizations in which guests, or templates, are used to create a molecular "impression" through incorporation within the infrastructure of appropriately juxtaposed ionic, hydrogen-bonding, or other noncovalent loci.[4,5] Typically organic guests are used as the template from which, after its removal, the cavity, the shape, and the directivity of the host's binding site are frozen for subsequent re-recognition of structurally related guests. Zimmerman et al.[6] developed a novel monomolecular imprinting process,[7] whereby porphyrin-cored dendrimers[8] having terminal alkene units were initially created, and subsequent alkene cross-linking gave the host–guest combination; porphyrin removal thus created the desired cavity possessing the desired recognition sites. van Koten and co-workers[9] employed this technique for the creation of a 69-membered macrocycle that reversibly accepts a pre-assembled platinum triad. Such host–guest molecular recognition generally relies on intermolecular assembly of components. Can the self-assembly process occur by an intramolecular mechanism in which a macromolecular skeleton has multiple ligands capable of reversible assembly–disassembly[10] which is triggered by the presence of metal ions? We herein describe a simple method allowing molecular nanofabrication by such a procedure.

Based on our previous work[11–13] concerning the hexameric self-assembly of *meta*-bis(terpyridinyl)arenes having the critical 120° angle with respect to the two ligating moieties, we noted that the Fe^{II} hexamer is more sensitive to basic conditions[14] compared to the more robust Ru^{II} analogue; thus under basic conditions, demetalation quantitatively regenerated the starting bis-ligand. Colasson and Sauvage[15] have similarly shown that the related [tpy_2Cu] (tpy = terpyridine) complex can also be destroyed by KCN. Such a facile disassembly process coupled with the high-yield hexamer macrocyclization suggested the possibly of reversible assembly in an appropriate molecular nanotemplate. Herein, we describe a reversible, assembly–disassembly procedure involving a hexametallomacrocycle containing twelve terpyridine groups enclosed within a 114-membered macrocyclic structure (Figure 1).

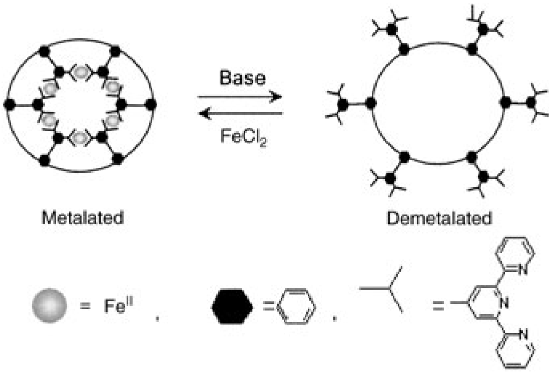

Figure 1. Reversible metalation–demetalation facilitates templated hexamer formation.

The design of the initial bis(terpyridine) ligand was facilitated by molecular modeling simulations (Figure 2) which were used to optimize the requisite alkyl chain length and thus the final ring circumference. Subsequently, oct-7-

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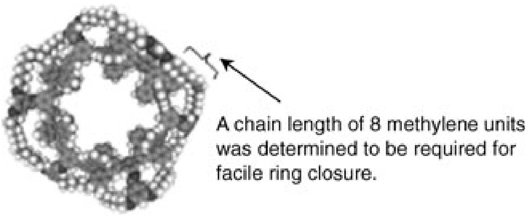
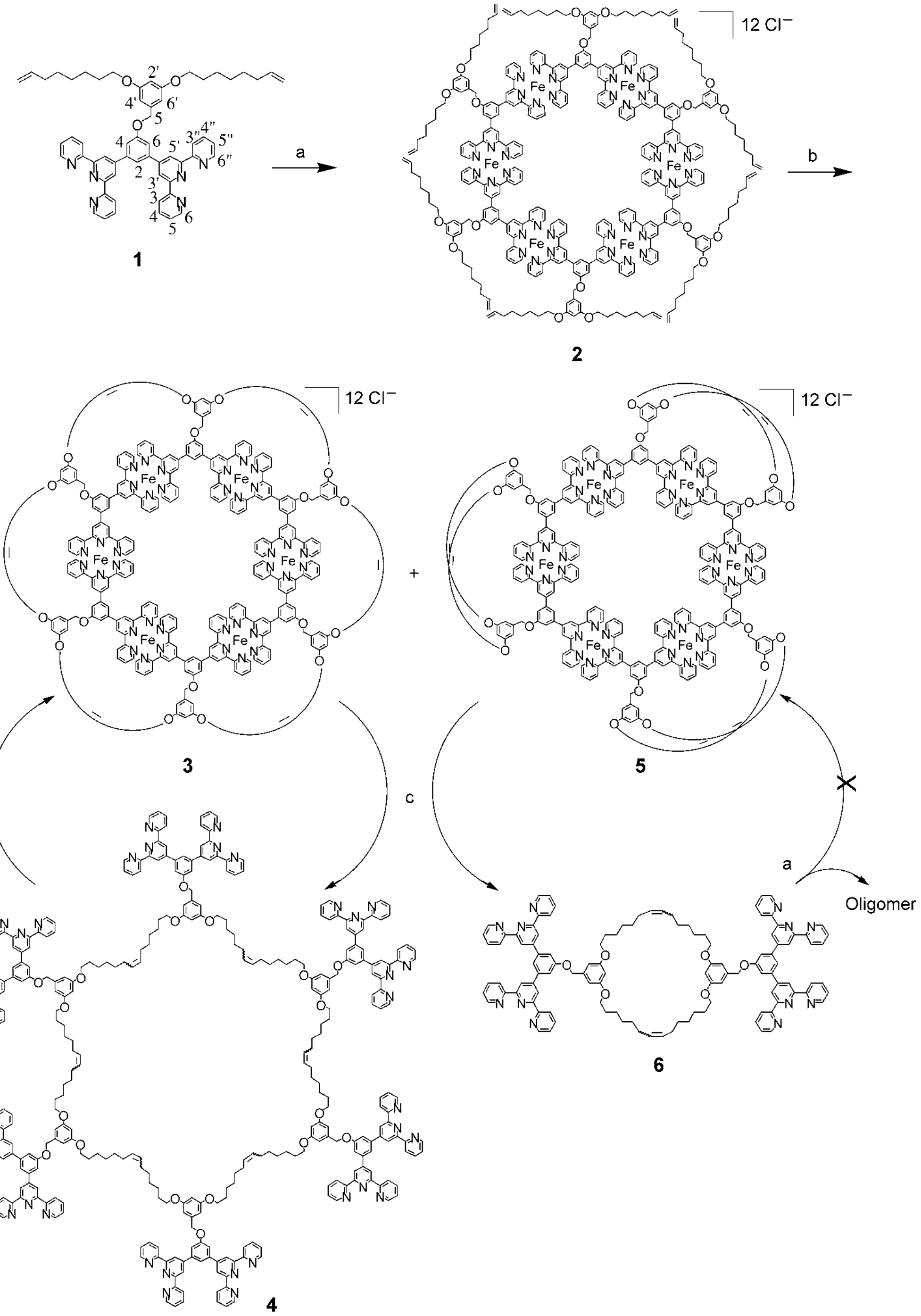


Figure 2. Computer generated molecular model of the templated hexamer **3**.

enyl groups were attached to a bis(terpyridinylphenol) to yield (82%) the alkene-modified ligand **1**.[16] This ligand was then treated (Scheme 1) with $FeCl_2$ in MeOH to form a deep purple solution, from which the heliotrope, microcrystalline hexamer **2** was isolated (91%) and confirmed (^{1}H NMR spectroscopy) by the downfield shift of the 3′,5′-tpy*H* (s; $\delta = 9.79$, $\Delta\delta = +0.96$ ppm), an upfield shift for the 6,6″-tpy*H* (d $J = 4.8$ Hz; $\delta = 7.33$, $\Delta\delta = -1.44$ ppm), and the shift of 4,6-Ar*H* positions (s; $\delta = 8.27$, $\Delta\delta = +0.66$ ppm) upon complexation. The distinct singlets for the external 4′,6′-Bn*H* and

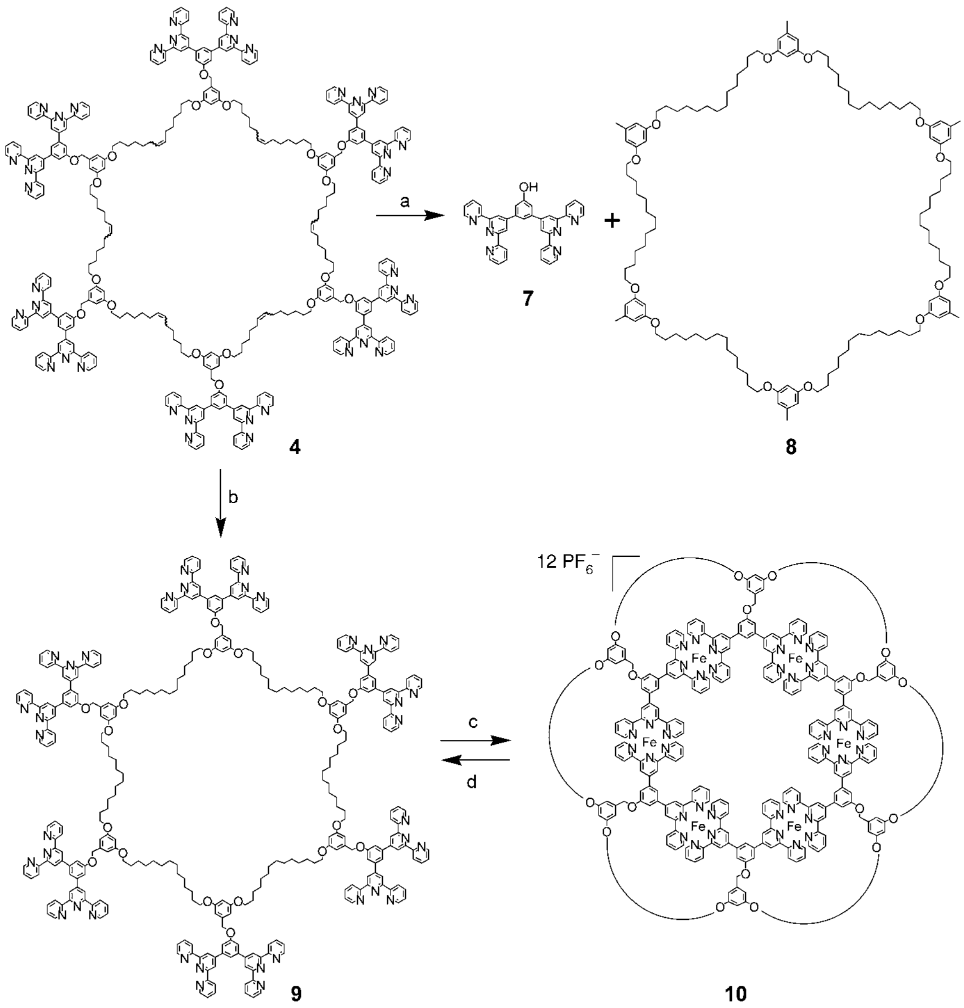


Scheme 1. a) $FeCl_2$, MeOH; b) $[PhCH{=}Ru(PCy)_2Cl_2]$ (Grubbs' catalyst), CH_2Cl_2; c) K_2CO_3, DMF.

benzylic protons support the symmetric, homogenous hexamer **2**, which was completely soluble in most of the common organic solvents.

Hexamer **2** was subsequently cross-linked using Grubbs' catalyst[6,9,17,18] to generate two major products: the desired purple, microcrystalline, inner macrocyclic complex **3**, which has the 114-membered, hexaolefinic ethereal outer superstructure, as well as the isomeric by-product **5** (Scheme 1). Success of the cross-linking reaction was demonstrated (^{1}H NMR spectroscopy) by the disappearance of the terminal alkene signals at $\delta = 5.80$–5.71 and 4.98–4.73 ppm along with the appearance of a new signal at $\delta = 5.62$ ppm for the formation of a new double bond as a mixture of *E* and *Z* isomers. Owing to the isomeric nature of **3** and **5**, quantitative demetalation (with K_2CO_3, DMF) of this crude mixture was initially confirmed by the total loss of coloration, indicative of the disassembly of the hexameric core. The resultant white solid, comprised the two major components **4** and **6**, which could be readily separated by preparative thin layer chromatography (TLC; Al_2O_3) eluting with a 3:1 mixture of EtOAc and hexane. In the ^{1}H NMR spectrum, the expected macrocycle **4** gave rise to a triplet at $\delta = 5.36$ ppm confirming the presence of the double bonds as well other signature resonance signals and in the mass spectrum **4** gave a definite peak at *m*/*z* 2612.8 (ESI-MS) for $(M+2H)^{2+}$. The nominal dimeric byproduct **6**, generated from **5**, was also separated and confirmed by NMR spectroscopy and ESI-MS. The cross-linking reaction greatly depends upon the concentration of hexamer **2**; in general, it was found that concentrations greater than 10^{-4} M generated more complex mixtures.[19] Subsequent treatment of pure hexa-bis(terpyridine) macrocycle **4** with Fe^{II} regenerated the purple microcrystalline **3**, which was readily demetalated (K_2CO_3, DMF) again to recover the original ligand **4** in a respectable overall conversion (85%; after chromatography).

To remove the structural complexity caused by the mixture of *cis* and *trans* olefinic configurations, the macrocycle ligand **4** was hydrogenated (Pd/C (5 or 10%), EtOH, THF (2/1, v/v)); however, olefin reduction was accompanied with the unwanted debenzylation affording (100%) the macrocycle **8**, as a viscous oil, and hydroxybis(terpyridine) **7**[16] that was identical to the original starting material **1** (Scheme 2). Whereas, the use of Raney-Ni[20] with hydrazine in EtOH gave rise to smooth reduction of the olefinic centers



Scheme 2. a) Pd/C (10%), H_2, EtOH, THF; b) 1. Raney-Ni, NH_2NH_2, EtOH, 2. K_2CO_3, EtOH; c) 1. $FeCl_2$, MeOH, 2. NH_4PF_6, MeOH; d) K_2CO_3, DMF.

and circumvented the unwanted debenzylation. The resulting a pale blue-green solution may get its color from traces of terpyridine-nickel complexes; refluxing this solution in ethanolic K_2CO_3 for 1 h subsequently afforded (> 90 %) the pure terpyridine-modified, ethereal macrocycle **9** after chromatography (Al_2O_3, EtOAc, hexane (3:1)). The reduced superstructure was confirmed (^{1}H NMR spectroscopy) by the disappearance of the resonance signal arising from olefinic protons. The structure was further supported by the mass peak at m/z 2641.5 (ESI-MS) for $(M+2\,Na)^{2+}$.

Treatment of **9** with $FeCl_2$ in MeOH gave a deep purple solid, which after column chromatography (SiO_2), eluting with a mixture of H_2O:MeCN:KNO_3 (1:7:1), and subsequent counterion exchange with PF_6^- gave hexamer **10** (80 %). Characteristic of this transformation, the 3′ and 5′ signals exhibited a 0.7 ppm downfield shift while the 6′ and 6″ signals resonate 1.4 ppm upfield relative to their positions in the free ligand (Figure 3). Quantitative disassembly of **10** with K_2CO_3 in DMF resulted in the reformation of the metal-free **9**, which was then again transformed back to complex **10**; assembled and disassembled samples were identical in all aspects to the original materials. Since there are no opportunities for structural repair in this assembly process through this mode of construction, there is a minor (ca. 3–5 %) loss in each reassembly phase. After removal of the pure regenerated hexamer by simple chromatography, all defective materials were simply treated with base to recover the original ligand. By using this recyclization procedure, overall yields can approach 100 %.

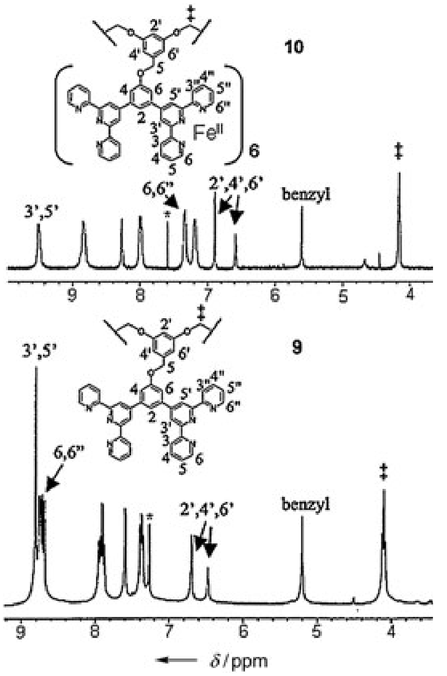


Figure 3. ^{1}H NMR spectra of the metalated hexamer template **10** (top; 750 MHz, $CDCl_3$* in CD_3CN) and the demetalated, polyterpyridine-modified, 114-membered cycloalkane **9** (bottom; 300 MHz, $CDCl_3$*).

In conclusion, it was shown that the assembly–disassembly of appropriately designed complexes within a macromolecular superstructure can readily occur by the use of a semilabile metal center. This nanofabrication would appear to be applicable to related high conversion complexation processes[21] by metal-ion driven imprinting procedures. The potential to craft nanoscale components that can repetitively self-assemble has ramifications for self-repairing mechanisms and architectural molecular morphism allowing access to new smart, tailored macromolecular materials.

Experimental Section

1: 3,5-di(octenyloxy)benzyloxybisterpyridine, see ref. [16].

2: m.p. > 300 °C; ^{1}H NMR (300 MHz; $CDCl_3/CD_3OD$: 1/1): $\delta =$ 9.79 (s, 4 H, Ar$H^{3',5'}$), 9.11 (s, 5 H, ArH^2 + Py$H^{3,3''}$), 8.27 (s, 2 H, Ar$H^{4,6}$), 8.01 (s, 4 H, Py$H^{4,4''}$), 7.33 (d, $J = 4.8$ Hz, 4 H, Py$H^{6,6''}$), 7.25 (s, 4 H, Py$H^{5,5''}$), 6.86 (s, 2 H, BnH), 6.53 (s, 1 H, BnH), 5.80–5.71 (m, 2 H, CCH=C), 5.59 (s, 2 H, OCH_2Ar), 4.98–4.73 (m, 4 H, C=CH_2), 4.04 (t, $J = 11.7$ Hz, 4 H, OCH_2), 2.02 (m, 4 H, CH_2), 1.80 (m, 4 H, CH_2), 1.49–1.25 ppm (m, 16 H, CH_2); ESI-MS (7469.42; $C_{354}H_{348}F_{72}Fe_6N_{36}O_{18}P_{12}$): m/z: 1722.6 $[M-4\,PF_6)^{4+}$, 1349.5 $[M-5\,PF_6]^{5+}$, 1100.3 $[M-6\,PF_6]^{6+}$, 922.1 $[M-7\,PF_6]^{7+}$, 789.0 $[M-8\,PF_6]^{8+}$, 685.1 $[M-9\,PF_6]^{9+}$, 602.3 $[M-10\,PF_6].^{10+}$

3: ^{1}H NMR (300 MHz; CD_3CN): $\delta = 9.48$ (s, 4 H, Ar$H^{3',5'}$), 8.83 (s, 5 H, ArH^2 + Py$H^{3,3''}$), 8.29 (s, 2 H, Ar$H^{4,6}$), 8.02 (s, 4 H, Py$H^{4,4''}$), 7.34 (s, 4 H, Py$H^{6,6''}$), 7.24 (s, 4 H, Py$H^{5,5''}$), 6.90 (s, 2 H, BnH), 6.62 (s, 1 H, BnH), 5.62 (m, 2 H, CH=CH), 5.43 (s, 2 H, OCH_2Ar), 4.18 and 4.07 (m, 4 H, OCH_2), 1.85 (m, 4 H, CH_2), 1.48–1.01 ppm (m, 16 H, CH_2).

4: m.p. 82–85 °C; ^{1}H NMR (300 MHz; $CDCl_3$): $\delta = 8.80$ (s, 4 H, Ar$H^{3',5'}$), 8.76 (d, 4 H, Py$H^{6,6''}$), 8.71 (d, 4 H, Py$H^{3,3''}$), 7.94 (s, 1 H, ArH^2), 7.90 (t, 4 H, Py$H^{4,4''}$), 7.58 (s, 2 H, Ar$H^{4,6}$), 7.39 (t, 4 H, Py$H^{5,5''}$), 6.71 (2 s, 2 H, BnH), 6.45 (m, 1 H, BnH), 5.36 (t, $J = 3.9$ Hz, 2 H, CH=CH/*trans* and *cis*), 5.19 (s, 2 H, OCH_2Ar), 4.07 (t, 4 H, OCH_2), 2.02 (m, 4 H, CH_2), 1.80 (m, 4 H, CH_2), 1.47 (m, 4 H, CH_2), 1.38 (m, 4 H, CH_2), 0.89 ppm (m, 4 H, CH_2); ^{13}C NMR (75 MHz; $CDCl_3$) $\delta = 160.4$, 160.1, 156.4, 156.2, 150.4, 149.4, 141.2, 139.2, 137.1, 130.8, 130.3, 124.1, 121.6, 119.5, 114.7, 108.1, 107.6 100.5, 70.5, 68.4, 32.2, 29.9, 29.1, 28.0, 27.6, 25.4 ppm; ESI-MS: (5226.46, $C_{342}H_{324}N_{36}O_{18}$), m/z 2612.8 $[M+2\,H]^{2+}$, 2635.3 $[M+2\,Na]^{2+}$, 2643.2 $[M+K+Na]^{2+}$, 1742.9 $[M+3\,H]^{3+}$, 1764.9 $[M+3\,Na]^{3+}$, 1774.2 $[M+Na+K]^{3+}$.

6: m.p. 80–83 °C; ^{1}H NMR (300 MHz; $CDCl_3$): $\delta = 8.78$ (s, 4 H, Ar$H^{3',5'}$), 8.74 (d, 4 H, Py$H^{6,6''}$), 8.70 (d, 4 H, Py$H^{3,3''}$), 7.93 (s, 1 H, ArH^2), 7.89 (t, 4 H, Py$H^{4,4''}$), 7.57 (s, 2 H, Ar$H^{4,6}$), 7.35 (t, 4 H, Py$H^{5,5''}$), 6.67 (2 s, 2 H, BnH), 6.44 (m, 1 H, BnH), 5.38 (t, 2 H, CH=CH/*trans* and *cis*), 5.18 (s, 2 H, OCH_2Ar), 3.98 (t, 4 H, OCH_2), 1.98 (m, 4 H, CH_2), 1.77 (m, 4 H, CH_2), 1.45 (m, 4 H, CH_2), 1.36 (m, 4 H, CH_2), 0.86 ppm (m, 4 H, CH_2). ESI-MS: (1746.19, $C_{114}H_{112}N_{12}O_6$), m/z 1743.2 $[M+H]^+$, 1765.0 $[M+Na]^+$,

9: m.p. 75–78 °C; ^{1}H NMR (300 MHz; $CDCl_3$): $\delta = 8.81$ (s, 4 H, Ar$H^{3',5'}$), 8.76 (d, 4 H, Py$H^{6,6''}$), 8.72 (d, 4 H, Py$H^{3,3''}$), 7.95 (s, 1 H, ArH^2), 7.91 (t, 4 H, Py$H^{4,4''}$), 7.60 (s, 2 H, Ar$H^{4,6}$), 7.37 (t, 4 H, Py$H^{5,5''}$), 6.70 (2 s, 2 H, BnH), 6.47 (m, 1 H, BnH), 5.21 (s, 2 H, OCH_2Ar), 4.10 (t, 4 H, OCH_2), 1.78 (m, 4 H, CH_2), 1.49 (m, 4 H, CH_2), 1.38 (m, 4 H, CH_2), 1.29 ppm (m, 8 H, CH_2). ^{13}C NMR (75 MHz; $CDCl_3$): $\delta = 160.7$, 156.4, 156.3, 150.4, 149.4, 141.2, 139.2, 137.1, 124.1, 121.6, 119.5, 114.7, 114.7, 106.9, 102.0, 100.2, 68.4, 28.7, 28.4, 28.2, 27.9, 25.2 ppm. ESI-MS: (5238.56, $C_{342}H_{336}N_{36}O_{18}$) m/z 2623.8 $[M+2\,H]^{2+}$, 2641.5 $[M+2\,Na]^{2+}$, 2652.5 $[M+K+Na]^{2+}$, 2659.7 $[M+2\,K]^{2+}$.

10: m.p. > 300 °C; ^{1}H NMR (750 MHz; CD_3CN): $\delta = 9.51$ (s, 4 H, Ar$H^{3',5'}$), 8.83 (s, 5 H, ArH^2 + Py$H^{3,3''}$), 8.27 (s, 2 H, Ar$H^{4,6}$), 7.99 (s, 4 H, Py$H^{4,4''}$), 7.33 (s, 4 H, Py$H^{6,6''}$), 7.18 (s, 4 H, Py$H^{5,5''}$), 6.89 (s, 2 H, BnH), 6.58 (s, 1 H, BnH), 5.60 (s, 2 H, OCH_2Ar), 4.16 (t, 4 H, OCH_2), 1.77 (m, 4 H, CH_2), 1.48 (m, 4 H, CH_2), 1.30 ppm (m, 12 H, CH_2). ESI-MS: data obtained using BF_4^- counterions; (6615.28, $C_{342}H_{336}B_{12}F_{48}Fe_6N_{36}O_{18}$), m/z 2118.5 $[M-3\,BF_4]^{3+}$, 1567.2 $[M-4\,BF_4]^{4+}$, 1236.5 $[M-5\,BF_4]^{5+}$, 1015.8 $[M-6\,BF_4]^{6+}$, 858.5 $[M-7\,BF_4]^{7+}$, 740.1 $[M-8\,BF_4]^{8+}$, 648.1

$[M-9\,BF_4]^{9+}$, 574.8 $[M-10\,BF_4]^{10+}$, 514.7 $[M-11\,BF_4]^{11+}$, 464.3 $[M-12\,BF_4]^{12+}$.

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