Ferrocene-Modified Artificial Ditopic Nucleobase Receptors Capable of Serving Both Hydrogen-Bonding and π-Stacking Interactions

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Ferrocene-modified artificial ditopic nucleobase receptors were designed and synthesized. The ditopic receptors possess two hydrogen-bonding and one π-stacking interaction sites that act simultaneously for the binding to 1-butylthymine utilizing the pivot character of the ferrocene skeleton. Diamidopyridine was chosen for the hydrogen-bonding moiety, and 2,7-disubstituted pyrene was used for π-stacking one. The ditopic receptors bound 1-butylthymine, and the stoichiometry for the complexation was found to be 1:2 in $CDCl_3$. In the ^1H NMR spectrum of the mixture for the receptors and 1-butylthymine, large downfield shifts of the NH protons on both diamidopyridine and 1-butylthymine revealed the complementary hydrogen bonds between them, while upfield shifts were observed for CH protons of the pyrene and the thymine nuclei reflecting from the close approach of the bound 1-butylthymine to the pyrene. Binding affinities of the ditopic receptors for 1-butylthymine were discussed on the basis of the total association constants.

Introduction

Self-assembly based on synthetic molecules has been becoming a fascinating field in supramolecular chemistry.[1] The systems often contain rigid molecules as a component because the entropic disadvantage due to the freeze of the conformation of the component molecules must be diminished during the complexation. The naturally occurring assembling systems, such as DNA and protein, however, utilize moderately rigid but still flexible components, so that the systems are capable of responding to external physical and/or chemical stimuli.[2]

In our successive model studies on molecular recognition,[3] our initial goal in this area described above is to develop the cooperative, stimuli-responsive self-assembling systems of DNA-relevant molecules. Thus, we sought to construct novel nucleobase receptors in which both hydrogen-bonding and π-stacking interactions can operate simultaneously and in which the conformational flexibility of the receptors would be restricted so that the recognition mode is well-defined.[4] With this in mind, we have already reported ferrocene-modified artificial nucleobase receptors, *ferroceptors* (ferrocene + receptors).[5] To extend this approach to the self-assembling systems, bifunctional ferroceptors will be needed. In this paper, we report molecular design and molecular recognition abilities of ferrocene-modified artificial ditopic nucleobase receptors.

Results and Discussion

Molecular Design and Synthesis. The molecular design of monotopic ferroceptors was fully described in

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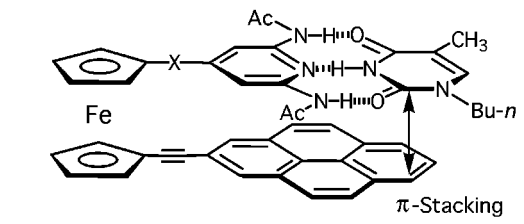
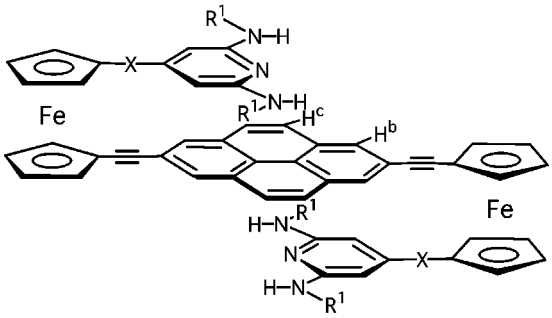
Scheme 1



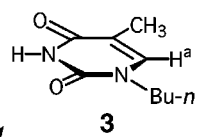
1 X = -CH_2O- **1•3** K_a = 1.7±0.1 X 10^3 M^{-1}

2 X = -C≡C- **2•3** K_a = 1.8±0.1 X 10^3 M^{-1}

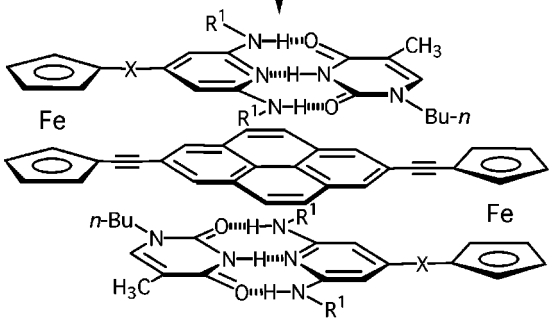


4a R^1 = COC_7H_{15}-*n*, X = -CH_2O-

4b R^1 = COC_7H_{15}-*n*, X = -C≡C-



3



4a•3 K_t = 6.7±0.3 X 10^6 M^{-2}

4b•3 K_t = 2.5±0.3 X 10^7 M^{-2}

the previous paper.[5a] The binding affinities of the monotopic ferroceptors to 1-butylthymine were dependent on the aromatic structures and the direction of an expanse of π-plane. This was demonstrated by the association constants of 2-ethynylpyrene-linked ferroceptors **1** and **2** compared to those of 1-ethynylpyrene-linked ones (ca. two times). These results are satisfactorily explained by the increased probability of the close approach of the aromatic rings of the ferroceptors to the π-plane of the bound 1-butylthymine **3**, depicted in Scheme 1. Taking into account the above points, we designed ferrocene-modified artificial ditopic nucleobase receptors **4**, in which two hydrogen-bonding moieties were connected to the pyrene ring at the 2 and 7 positions.

The oxymethylene-linked ditopic ferroceptor **4a** was synthesized by Mitsunobu[6] and Sonogashira[7] reactions in the key steps. Mitsunobu reaction of 1-(hydroxymethyl)-1′-iodoferrocene (**5**) with 2,6-di-*n*-octamido-4-pyridone (**14**) gave **6**, which was ethynylated by the Sonogashira reaction followed by deprotection of the acetylene terminal to afford **8**. Further Sonogashira reaction of 2 equiv of **8** with 2,7-dibromopyrene (**18**) produced **4a**. On the other hand, ethynediyl-linked ditopic ferroceptor **4b** was prepared from 1,1′-diiodoferrocene (**9**) by sequential Sonogashira reactions with 2,6-di-*n*-octamido-4-ethynylpyridine (**17**) and 2,7-diethynylpyrene (**20**). Reference compound **11** was also derived from **9** and **20** (Scheme 2).

Assignment of the Pyrene Protons by NOE Experiments. Complete assignment of the ^{1}H NMR signals of both the ditopic ferroceptors **4** and 1-butylthymine (**3**) is crucial for the binding studies. The two sets of singlet for the symmetrically 2,7-disubstituted pyrene protons (H^b and H^c in Scheme 1), however, remained to be assigned. Thus, we measured NOEs (nuclear Overhauser effect) by use of the simple model compound **19** because the chemical shifts of the pyrene protons of **4** are almost identical to those of **19** and **20**. During the irradiation for the methyl protons of **19**, NOE enhancements were observed for both peaks of OH protons (+3.6%) and of the pyrene protons at the lower field protons (8.22 ppm; +1.1%), but never for the upper field protons (8.00 ppm). Furthermore, during irradiation for the pyrene protons at lower field, NOE enhancement was observed at the methyl protons. The NOE experiments demonstrated that the singlet peak that appeared at lower field was assigned to the pyrene-H^b and the peak at upper field was H^c.

Electronic Absorption Spectra of the Ditopic Ferroceptors in the Presence of the Thymine Derivative. Electronic absorption spectra gave some important information for the complexation between the ditopic ferroceptors **4** and the thymine derivative **3**. Thus, the absorption spectra of **4a** changed upon addition of **3** in $CHCl_3$. When **3** was added incrementally to the $CHCl_3$ solution of **4a**, red shifts of the longest wavebands and hypochromism at 321 and 339 nm of **4a** were observed. Similar changes were also seen for **4b** in place of **4a**, but little for the reference compound **11** lacking in hydrogen-bonding sites (Figure 1). These phenomena resemble the absorbance decrease of nucleobases during the change from single-stranded to double-helical DNA that results from the stacking of the aromatic bases. Thus, there is a strong presumption for the presence of the through-space interactions, π-stacking, and/or van der Waals interactions between the pyrene moieties of **4** and the bound **3**.[8]

Complexation-Induced Shifts for the Protons of the Ditopic Ferroceptors and the Thymine Derivative. The details of interactions for the ditopic ferroceptors **4** with 1-butylthymine (**3**) were investigated by ^{1}H NMR at 400 MHz in $CDCl_3$. Treatment of **4a** (2.0 mM) with **3** (4.0 mM) in $CDCl_3$ resulted in several characteristic changes in the spectrum (Figure 2). Large downfield shifts were observed for both the NH protons of **4a** (1.73 ppm) and **3** (2.20 ppm), indicating the formation of a

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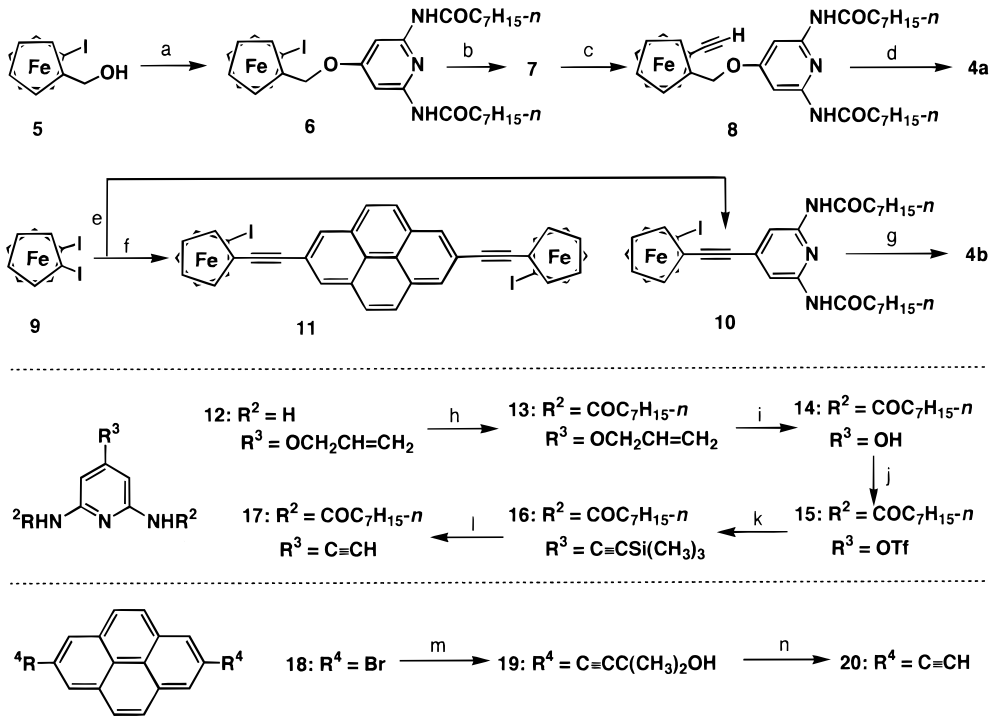
Scheme 2[a]



[a] Key: (a) **14**, DEAD, PPh_3, THF; (b) (trimethylsilyl)acetylene, $(Ph_3P)_2PdCl_2$, $Cu(OAc)_2 \cdot H_2O$, *i*-Pr_2NH; (c) KF, H_2O, DMSO; (d) **18**, $(Ph_3P)_4Pd$, $Cu(OAc)_2 \cdot H_2O$, morpholine, DMF; (e) **17**, $(Ph_3P)_4Pd$, $Cu(OAc)_2 \cdot H_2O$, *i*-Pr_2NH; (f) **20**, $(Ph_3P)_4Pd$, CuI, morpholine; (g) **20**, $(Ph_3P)_4Pd$, CuI, morpholine; (h) *n*-octanoyl chloride, Et_3N, CH_2Cl_2; (i) $(Ph_3P)_3RhCl$, DABCO, CH_3CN, EtOH, H_2O; (j) trifuluoromethanesulfonic anhydride, pyridine; (k) (trimethylsillyl)acetylene, $(Ph_3P)_2PdCl_2$, Et_3N, DMF; (l) tetra-*n*-butylammonium fluoride, H_2O, THF; (m) 2-methyl-3-butyn-2-ol, $(Ph_3P)_2PdCl_2$, CuI, morpholine; (n) NaH, toluene.

multipoint hydrogen-bonded complex between **4a** and **3**. On the other hand, CH protons of the pyrene nucleus (H^b, 0.29 ppm; H^c, 0.19 ppm) of **4a**, **3**-H^a (0.12 ppm), and **3**-NCH_2 (0.12 ppm) were shifted upfield, which might be attributed to the diamagnetic anisotropy produced by the close approach of the bound **3** to the pyrene ring of **4a**. The significant but rather small upfield shifts illustrated the free rotation of the cyclopentadienyl (Cp) rings of ferrocene even for the complex.[5a] This type of complexation-induced shifts were observed also with **4b** in place of **4a**. Indeed, both the downfield shifts (**4b**-NH, 2.18 ppm; **3**-NH, 1.94 ppm) and the upfield shifts (**4b**-H^b, 0.34 ppm; **4b**-H^c, 0.15 ppm; **3**-H^a, 0.09 ppm; and **3**-NCH_2, 0.09 ppm) revealed the complex formation similar to that speculated between **4a** and **3**. In both cases, the **3**-induced shift of H^b of **4** was observed further upfield than that of H^c, suggesting a possible conformation of the complex in which the bound **3** was located on the terminal position of the pyrene nucleus of **4** (i.e., above H^b) as depicted in Scheme 1.

Quantitative Studies for the Complexation. The evaluation of stoichiometry and association constants for the complexation was also carried out by ^1H NMR (400 MHz) in $CDCl_3$ at room temperature (298 K). The 1:2 stoichiometry (**4·3**) was confirmed by the continuous variation (Job) plots that contained a maximum at a mole ratio of 0.33 for **4** where [**4**] + [**3**] is maintained at a constant level.[9] Total association constants (K_t) for the complexes (**3·4·3**) were determined from ^1H NMR titration data by using Foster−Fife analysis of the shifts in δ_{NH} for **4** (under conditions of constant [**4**] with varying [**3**]).[10] The association constant between **4a** and 2 equiv of **3** was determined to be $6.7 \pm 0.3 \times 10^6$ M^{-2}, and that for **4b** was $2.5 \pm 0.3 \times 10^7$ M^{-2}. Thus, the free energy changes ($-\Delta G_{298}$) for the complexation with 2 equiv of **3** in $CDCl_3$ were 38.9 kJ/mol for **4a** and 42.2 kJ/mol for **4b** (Scheme 1). These values were ca. 2.1−2.3 times larger than those for the monotopic ferroceptors ($-\Delta G_{298} = 18.5$ and 18.6 kJ/mol for **1·3** and **2·3**, respectively).[5a] The added stabilization ($-\Delta G_{ditopic} + 2\Delta G_{monotopic}$: the cooperative effect) is 1.9 and 5.0 kJ/mol for **4a** and **4b**, respectively. While these numbers are small relative to the overall binding energy, within experimental errors, the results suggested that small cooperative binding may exist for the three-component complex formation for the ditopic ferroceptors.[11] The origin for the cooperative effect

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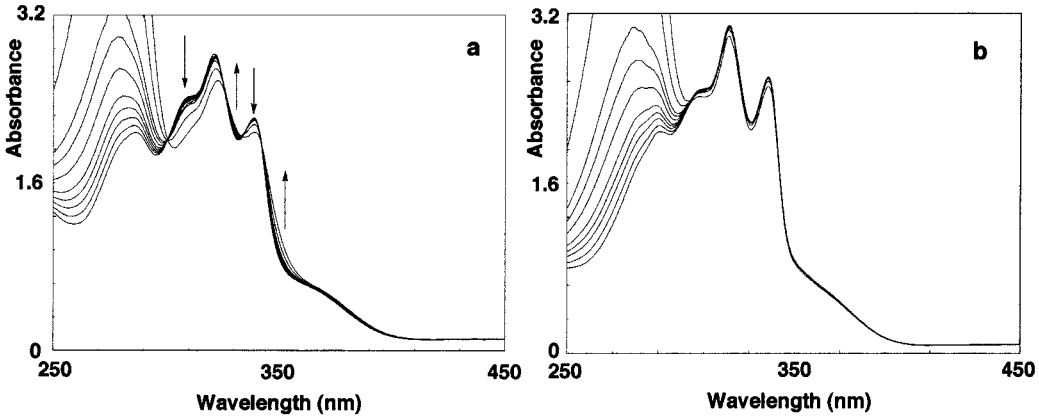

Figure 1. Electronic absorption spectra of $CHCl_3$ solution of (a) **4a** (0.03 mM) and (b) **11** (0.03 mM) in the presence of **3** (0−20 equiv).

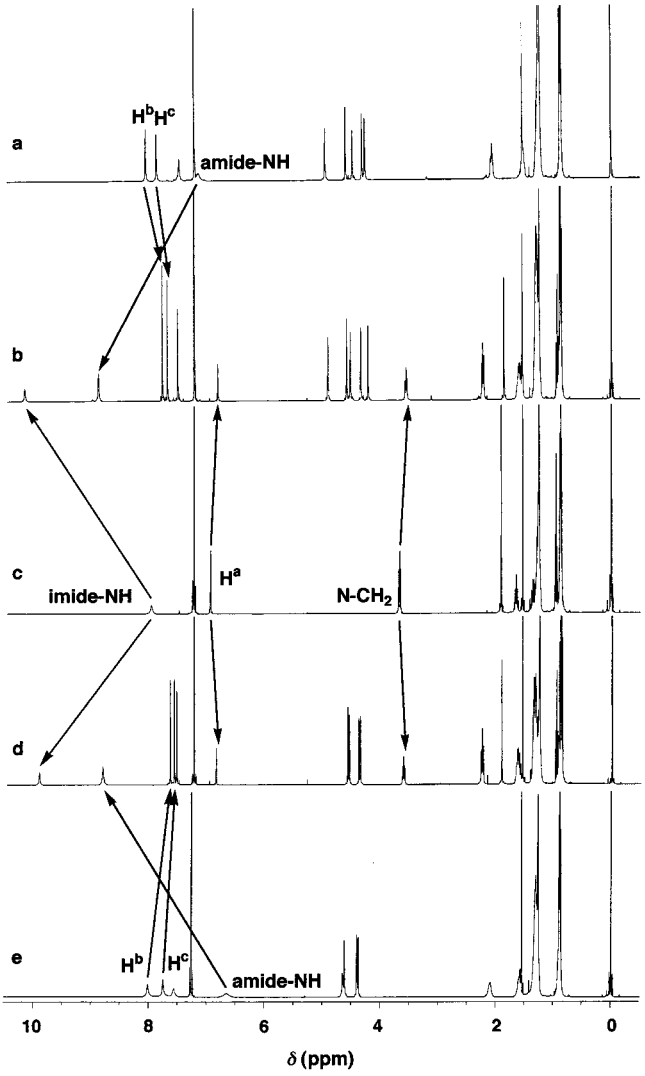

Figure 2. ^{1}H NMR spectra (400 MHz) of (a) **4a** (2.0 mM), (b) **3·4a·3**, (c) **3** (4.0 mM), (d) **3·4b·3**, and (e) **4b** (2.0 mM) in $CDCl_3$ at 25 °C. See Scheme 1 for proton labeling.

in the ferroceptors is still unknown and remains to be elucidated.

Conclusions

We developed novel ferrocene-modified artificial ditopic nucleobase receptors, ditopic ferroceptors. The binding mode of the ditopic ferroceptors for thymine derivatives was characterized by use of ^{1}H NMR spectroscopy. The two hydrogen-bonding sites of the ferroceptors were found to act cooperatively to a small extent for the binding to the thymine derivative as well as additional π-stacking interactions. We are currently investigating the introduction of a metal cation recognition site in the ferrocene skeleton in order to add allosteric behavior to the ferroceptors. In the future, bifunctionalization of both the allosteric ferroceptors and the substrates will create cooperative self-assembly of more than one biologically relevant species responding to external chemical stimuli.

Experimental Section

Instrumentation. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. For FAB mass experiments, Xe was used as the atom beam accelerated to 8 keV. Melting points are uncorrected.

Materials. 1-*n*-Butylthymine[12] (**3**), 1-(hydroxymethyl)-1′-iodoferrocene[5a] (**5**), 1,1′-diiodoferrocene[13] (**9**), 4-allyloxy-2,6-diaminopyridine[14] (**12**), and 2,7-dibromopyrene[15] (**18**) were prepared according to literature procedures. Other starting materials were all commercially available.

Methods for the Evaluation of Stoichiometry and Association Constants. The Job plot of [complex] vs mole fraction of the receptor **4** for the complexation of **4** and **3** was obtained by ^{1}H NMR in $CDCl_3$ at 25 °C under conditions where [**4a**] + [**3**] is maintained at 1.5 mM and [**4b**] + [**3**] is at 1.0 mM.[9] The relative concentration of a complex [complex (rel)] in $CDCl_3$ was evaluated from $\Delta\delta_{obsd}$ for the **3**-NH, according to the equation, [complex (rel)] = $\Delta\delta_{obsd}$[receptor]$_t$ (t = total; obsd = observed; sat. = saturated).

Determination of total association constants (K_t) was carried out under Benesi−Hildebrand conditions at 25 °C in $CDCl_3$.[10] The concentrations of **4** and **3** were 0.025 and 0.5−1.0 mM,

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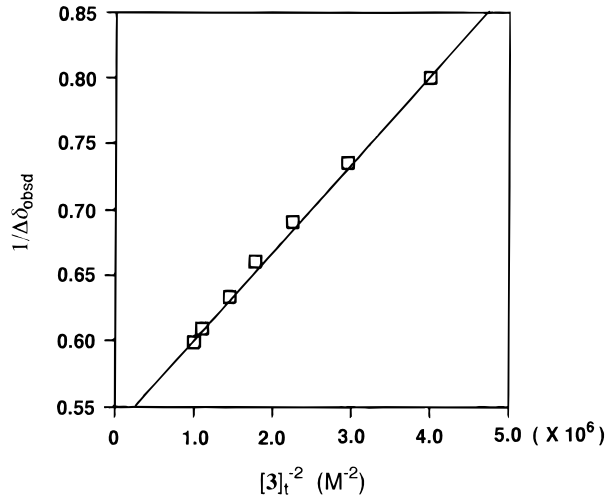

Figure 3. Benesi−Hildebrand plot for **4a** and **3**.

respectively. The chemical shifts of the **4**-NH protons were monitored as a function of **3** concentration. In each case, the double reciprocal plots according to the equation, $1/\Delta\delta_{obsd} = 1/\Delta\delta_{sat.} + 1/\Delta\delta_{sat.} K_t[\mathbf{3}]_t^2$ gave good linearity with a correlation coefficient $r \geq 0.99$ (Figure 3).

4-Allyloxy-2,6-di-*n*-octamidopyridine (13). To a CH_2Cl_2 (300 mL) solution of 4-allyloxy-2,6-diaminopyridine[14] (**12**; 2.75 g, 16.6 mmol) and Et_3N (9.3 mL) was added *n*-octanoyl chloride (5.67 g, 34.9 mmol) dropwise at 0 °C. The reaction mixture was stirred at room temperature for 6 h and washed with water. After removal of the solvent, the residue was chromatographed (silica gel; eluent, CH_2Cl_2) to give **13**: yield 85% (5.90 g); oil; IR (KBr) 1678, 1439 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.57 (s, 2 H), 7.48 (s, 2 H), 6.06−5.96 (m, 1 H), 5.43 (dd, J = 14.2, 1.5 Hz, 1 H), 5.30 (dd, J = 10.5, 1.5 Hz, 1 H), 4.61 (d, J = 5.4 Hz, 2 H), 2.35 (t, J = 7.3 Hz, 4 H), 1.74−1.67 (m, 4 H), 1.38−1.27 (m, 16 H), 0.88 (t, J = 6.8 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 171.84, 168.19, 150.58, 131.76, 118.14, 96.30, 68.84, 37.46, 31.49, 29.02, 28.89, 25.17, 22.44, 13.88; FABMS (in 3-nitrobenzyl alcohol) *m/e* (rel intensity) 418 (MH^+, 100).

2,6-Di-*n*-octamido-4-pyridone (14). A mixture of **13** (2.67 g, 6.74 mmol), $(Ph_3P)_3RhCl$ (370 mg, 0.41 mmol), and DABCO (59 mg, 0.53 mmol) in $CH_3CN-EtOH-H_2O$ (23 + 23 + 23 mL) was stirred at 80 °C for 15 h. After removal of the solvent, the residue was chromatographed (silica gel; eluent, $CHCl_3$/AcOEt 10:1) to give **14**: yield 78% (1.99 g); mp 162−164 °C; IR (KBr) 1659, 1462, 1439 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.50 (s, 1 H), 9.76 (s, 2 H), 7.25 (s, 2 H), 2.33(t, J = 7.6 Hz, 4 H), 1.55−1.50 (m, 4 H), 1.37−1.21 (m, 16 H), 0.88 (t, J = 6.6 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 172.64, 168.24, 150.11, 98.20, 38.03, 31.64, 29.14, 28.98, 25.50, 22.61, 14.07; FABMS (in 3-nitrobenzyl alcohol) *m/e* (rel intensity) 378 (MH^+, 100). Anal. Calcd for $C_{21}H_{35}N_3O_3$: C, 66.81; H, 9.34; N, 11.13. Found: C, 66.56; H, 9.74; N, 10.81.

4-(2,6-Di-*n*-octamidopyridyl) Trifluoromethanesulfonate (15). To a pyridine (5.5 mL) solution of **14** (592 mg, 1.57 mmol) was added trifluoromethanesulfonic anhydride (575 mg, 6.23 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 3 h. After removal of the solvent, the residue was dissolved in water and extracted with Et_2O. The Et_2O extract was evaporated and chromatographed (silica gel; eluent, CH_2Cl_2) to give **15**: yield 94% (750 mg); mp 72−73 °C; IR (KBr) 1684, 1433, 1215 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.95 (s, 2 H), 7.71 (s, 2 H), 2.38 (t, J = 7.3 Hz, 4 H), 1.74−1.67 (m, 4 H), 1.38−1.29 (m, 16 H), 0.88 (t, J = 6.8 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 171.82, 158.60, 151.07, 118.57 (q, J_{C-F} = 320 Hz), 102.13, 37.70, 31.63, 29.09, 28.99, 25.04, 22.61, 14.07; FABMS (in 3-nitrobenzyl alcohol) *m/e* (rel intensity) 510 (MH^+, 100).

2,6-Di-*n*-octamido-4-[(trimethylsilyl)ethynyl]pyridine (16). To a DMF (5 mL) solution of **15** (664 mg, 1.30 mmol), $(Ph_3P)_2PdCl_2$ (73 mg, 0.10 mmol), and Et_3N (2.7 mL) was added (trimethylsilyl)acetylene (384 mg, 3.92 mmol) at room temperature. The reaction mixture was stirred at 80 °C for 8 h. After removal of the solvent, the residue was poured into water and extracted with Et_2O. The Et_2O extract was evaporated and chromatographed (silica gel; eluent, CH_2Cl_2) to give **16**: yield 99% (591 mg); oil; IR (KBr) 2168, 1680, 1552, 1416 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.98 (s, 2 H), 7.48 (s, 2 H), 2.36 (t, J = 7.3 Hz, 4 H), 1.75−1.67 (m, 4 H), 1.38−1.27 (m, 16 H), 0.88 (t, J = 6.8 Hz, 6 H), 0.23 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 171.79, 149.51, 135.35, 111.65, 102.13, 99.51, 37.30, 31.45, 28.95, 28.84, 25.12, 22.39, 13.85, −0.61; FABMS (in 3-nitrobenzyl alcohol) *m/e* (rel intensity) 458 (MH^+, 100).

2,6-Di-*n*-octamido-4-ethynylpyridine (17). To a THF (14 mL) solution of **16** (797 mg, 1.74 mmol) were added tetra-*n*-butylammonium fluoride (549 mg, 2.1 mmol) and a few drops of water. The reaction mixture was stirred at room temperature for 3 h. After removal of the solvent, the residue was poured into water and extracted with Et_2O. The Et_2O extract was evaporated and chromatographed (silica gel; eluent, CH_2Cl_2) to give **17**: yield 99% (665 mg); mp 84−86 °C; IR (KBr) 3400, 2080, 1709, 1670, 1566, 1427 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.02 (s, 2 H), 7.54 (br s, 2 H), 3.24 (s, 1 H), 2.37 (t, J = 7.3 Hz, 4 H), 1.75−1.67 (m, 4 H), 1.38−1.27 (m, 16 H), 0.88 (t, J = 6.6 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 171.52, 149.49, 134.79, 112.00, 81.48, 81.35, 37.83, 31.64, 29.14, 29.01, 25.31, 22.61, 14.08; FABMS (in 3-nitrobenzyl alcohol) *m/e* (rel intensity) 386 (MH^+, 100). Anal. Calcd for $C_{23}H_{35}N_3O_2$: C, 71.65; H, 9.15; N, 10.89. Found: C, 71.19; H, 9.42; N, 10.60.

2,7-Bis(3-hydroxy-3-methyl-1-butynyl)pyrene (19). To a morpholine (4.2 mL) suspension of 2,7-dibromopyrene[15] (**18**; 154 mg, 0.42 mmol), $(Ph_3P)_2PdCl_2$ (24 mg, 34 μmol), and CuI (6.5 mg, 34 μmol) was added 2-methyl-3-butyn-2-ol (150 mg, 1.8 mmol) at room temperature. The reaction mixture was stirred at 80 °C for 3 h. After removal of the solvent, the residue was dissolved in water and extracted with $CHCl_3$. The $CHCl_3$ extract was evaporated and chromatographed (silica gel; eluent, $CHCl_3$/AcOEt 20:1) to give **19**: yield 84% (130 mg); mp 290−293 °C; IR (KBr) 3396 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.22 (s, 4 H), 8.00 (s, 4 H), 2.11 (s, 2 H), 1.72 (s, 12 H); ^{13}C NMR ($CDCl_3$) δ 130.95, 128.07, 127.43, 123.71, 120.45, 94.43, 82.59, 65.77, 31.56; FABMS (in 3-nitrobenzyl alcohol) *m/e* (rel intensity) 366 (M^+, 60). Anal. Calcd for $C_{26}H_{22}O_2$: C, 85.22; H, 6.05. Found: C, 84.57; H, 5.97.

2,7-Diethynylpyrene (20). To NaH (1 mg, 25 μmol; commercial 60% dispersion was washed thoroughly with hexane prior to use) was added a toluene solution (2.0 mL) of **19** (70 mg, 0.21 mmol). The reaction mixture was heated to 110 °C immediately and stirred for 2 h at that temperature. After removal of the solvent, the residue was dissolved in water and extracted with $CHCl_3$. The $CHCl_3$ extract was evaporated and chromatographed (silica gel; eluent, CH_2Cl_2) to give **20**: yield 75% (30 mg); mp 211−214 °C; IR (KBr) 3282, 2108 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.30 (s, 4 H), 8.04 (s, 4 H), 3.27 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 131.08, 128.58, 127.56, 124.02, 119.99, 84.00, 77.89; FABMS (in 3-nitrobenzyl alcohol) *m/e* (rel intensity) 250 (M^+, 60). Anal. Calcd for $C_{20}H_{10}$: C, 95.97; H, 4.03. Found: C, 95.33; H, 3.81.

2,6-Di-*n*-octamido-4-[(1′-iodoferrocenyl)methoxy]pyridine (6). To a THF (45 mL) solution of 1-(hydroxymethyl)-1′-iodoferrocene[5a] (**5**; 870 mg, 2.54 mmol), **14** (1.15 g, 3.05 mmol) and triphenylphosphine (1.20 g, 3.31 mmol) was added diethyl azodicarboxylate (576 mg, 3.31 mmol) dropwise at room temperature. The mixture was stirred for 6 h at that temperature. After removal of the solvent, the residue was dissolved in water and extracted with Et_2O. The Et_2O extract was evaporated and chromatographed (silica gel; eluent, hexane/AcOEt 10:3) to give **6**: yield 66% (1.18 g); oil; IR (KBr) 1693 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.63 (br s, 2 H), 7.48 (br s, 2 H), 4.91 (s, 2 H), 4.43 (t, J = 1.8 Hz, 2 H), 4.32 (t, J = 1.8 Hz, 2 H), 4.23 (t, J = 1.8 Hz, 2 H), 4.18 (t, J = 1.8 Hz, 2 H), 2.36 (t, J = 7.6 Hz, 4 H), 1.75−1.67 (m, 4 H), 1.38−1.27 (m, 16 H), 0.88 (t, J = 6.8 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 171.68, 168.39, 150.47, 96.24, 82.92, 75.17, 71.80, 69.53, 66.03, 39.98, 37.84, 31.59, 29.10, 28.95, 25.28, 22.55, 14.05; FABMS (in 3-nitrobenzyl alcohol) *m/e* (rel intensity) 701 (M^+, 100).

2,6-Di-*n*-octamido-4-[[(1′-trimethylsilylethynyl)ferrocenyl]methoxy]pyridine (7). To an *i*-Pr_2NH (30 mL) solution of **6** (1.15 g, 1.64 mmol), $(Ph_3P)_2PdCl_2$ (70 mg, 0.10 mmol), and $Cu(OAc)_2 \cdot H_2O$ (20 mg, 0.10 mmol) was added (trimethylsilyl)-acetylene (483 mg, 4.91 mmol). The reaction mixture was stirred for 6 h at 80 °C. After removal of the solvent, the residue was dissolved in water and extracted with Et_2O. The Et_2O extract was evaporated and chromatographed (silica gel; eluent, hexane/AcOEt 10:3) to give **7**: yield 95% (1.05 g); oil; IR (KBr) 2150, 1689 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.72 (br s, 2 H), 7.63 (br s, 2 H), 4.93 (s, 2 H), 4.45 (t, J = 1.8 Hz, 2 H), 4.36 (t, J = 1.8 Hz, 2 H), 4.21−4.19 (m, 4 H), 2.32 (t, J = 7.3 Hz, 4 H), 1.73−1.65 (m, 4 H), 1.38−1.27 (m, 16 H), 0.88 (t, J = 6.8 Hz, 6 H), 0.20 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 171.64, 168.37, 150.45, 103.29, 96.33, 91.32, 81.74, 72.24, 70.91, 70.85, 69.40, 66.09, 65.60, 37.76, 31.57, 29.07, 28.94, 25.27, 22.52, 14.01, 0.08; FABMS (in 3-nitrobenzyl alcohol) *m/e* (rel intensity) 671 (M^+, 100).

2,6-Di-*n*-octamido-4-[(1′-ethynylferrocenyl)methoxy]-pyridine (8). To a DMSO (12 mL) solution of **7** (873 mg, 1.30 mmol) was added a saturated KF aqueous solution (10 mL) at room temperature. The reaction mixture was stirred at that temperature for 2 h, poured into water, and extracted with Et_2O. The Et_2O extract was evaporated and chromatographed (silica gel; eluent, hexane/AcOEt 10:3) to give **8**: yield 92% (714 mg); oil; IR (KBr) 3269, 2108, 1689 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.63 (s, 2 H), 7.46 (s, 2 H), 4.93 (s, 2 H), 4.48 (t, J = 1.8 Hz, 2 H), 4.41 (t, J = 1.8 Hz, 2 H), 4.25−4.23 (m, 4 H), 3.06 (s, 1 H), 2.36 (t, J = 7.3 Hz, 4 H), 1.73−1.67 (m, 4 H), 1.38−1.27 (m, 16 H), 0.88 (t, J = 6.6 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 171.78, 168.37, 150.52, 96.19, 81.51, 80.19, 75.40, 72.01, 70.70, 70.27, 69.10, 66.52, 64.89, 37.38, 31.42, 28.95, 28.82, 25.14, 22.39, 13.90; FABMS (in 3-nitrobenzyl alcohol) *m/e* (rel intensity) 599 (M^+, 86).

Ditopic Ferroceptor 4a. A mixture of **8** (690 mg, 1.16 mmol), **18**[15] (190 mg, 0.53 mmol), $(Ph_3P)_4Pd$ (49 mg, 42 μmol), and $Cu(OAc)_2 \cdot H_2O$ (8.4 mg, 42 μmol) in morpholine−DMF (3 + 2 mL) was stirred at 70 °C for 6 h. After removal of the solvent, the residue was poured into water and extracted with CH_2Cl_2. The CH_2Cl_2 extract was evaporated, and the resulting precipitate was washed with AcOEt and Et_2O to afford **4a**: yield 27% (384 mg); mp 170−171 °C; IR (KBr) 3394, 2214, 1672 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.10 (s, 4 H), 7.91 (s, 4 H), 7.52 (br s, 4 H), 7.20 (br s, 4 H), 5.00 (s, 4 H), 4.64 (t, J = 1.8 Hz, 4 H), 4.51 (t, J = 1.8 Hz, 4 H), 4.35 (t, J = 1.8 Hz, 4 H), 4.30 (t, J = 1.8 Hz, 4 H), 2.08 (t, J = 7.3 Hz, 8 H), 1.60−1.53 (m, 8 H), 1.30−1.26 (m, 32 H), 0.88 (t, J = 6.8 Hz, 12 H); ^{13}C NMR ($CDCl_3$) δ 171.33, 168.49, 150.19, 130.81, 127.79, 127.32, 123.43, 121.59, 96.24, 87.19, 72.15, 69.94, 69.58, 65.55, 37.56, 31.65, 29.09, 29.00, 25.09, 22.62, 14.11; FABMS (in 3-nitrobenzyl alcohol) *m/e* (rel intensity) 1397 (M^+, 100). Anal. Calcd for $C_{84}H_{96}N_6O_6Fe_2$: C, 72.20; H, 6.92; N, 6.01. Found: C, 71.68; H, 6.98; N, 5.73.

2,6-Di-*n*-octamido-4-[(1′-iodoferrocenyl)ethynyl]pyridine (10). An *i*-Pr_2NH solution (40 mL) of 1,1′-diiodoferrocene[13] (**9**; 4.88 g, 11.2 mmol), $(Ph_3P)_4Pd$ (103 mg, 89 μmol), $Cu(OAc)_2 \cdot H_2O$ (17.8 mg, 89 μmol), and **17** (430 mg, 1.11 mmol) was stirred at 55 °C for 3 h. After removal of the solvent, the residue was poured into water and extracted with CH_2Cl_2. The CH_2Cl_2 extract was evaporated and chromatographed (silica gel; eluent, CH_2Cl_2) to give **10**: yield 59% (454 mg); mp 89−90 °C; IR (KBr) 3290, 2214, 1678 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.03 (s, 2 H), 7.51 (s, 2 H), 4.51 (t, J = 1.8 Hz, 2 H), 4.47 (t, J = 1.8 Hz, 2 H), 4.29 (t, J = 1.8 Hz, 2 H), 4.24 (t, J = 1.8 Hz, 2 H), 2.38 (t, J = 7.3 Hz, 4 H), 1.76−1.69 (m, 4 H), 1.38−1.25 (m, 16 H), 0.89 (t, J = 6.6 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 171.64, 149.43, 136.28, 111.06, 92.70, 85.13, 76.23, 74.19, 72.69, 71.04, 65.70, 40.85, 37.59, 31.54, 29.04, 28.92, 25.22, 22.49, 14.00; FABMS (in 3-nitrobenzyl alcohol) *m/e* (rel intensity) 695 (M^+, 100). Anal. Calcd for $C_{33}H_{42}N_3O_2FeI$: C, 56.99; H, 6.09; N, 6.04. Found: C, 57.34; H, 6.22; N, 5.76.

Ditopic Ferroceptor 4b. A morpholine (1.5 mL) solution of **10** (184 mg, 0.27 mmol), **20** (23 mg, 0.10 mmol), $(Ph_3P)_4Pd$ (9.5 mg, 8.2 μmol), and CuI (1.6 mg, 8.2 μmol) was stirred at 70 °C for 10 h. After removal of the solvent, the residue was poured into water and extracted with $CHCl_3$. The $CHCl_3$ extract was evaporated and chromatographed (silica gel; eluent, $CHCl_3$) to give **4b**: yield 30% (43 mg); mp 165−167 °C; IR (KBr) 3294, 2214, 1691 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.65 (s, 4 H), 8.13 (s, 4 H), 7.92 (s, 4 H), 7.62 (s, 4 H), 4.78 (br s, 4 H), 4.72 (br s, 4 H), 4.53 (br s, 4 H), 4.50 (br s, 4 H), 2.17 (t, J = 7.3 Hz, 8 H), 1.45−1.26 (m, 8 H), 1.25−1.10 (m, 32 H), 0.83 (t, J = 6.6 Hz, 12 H); ^{13}C NMR ($CDCl_3$) δ 170.94, 148.46, 136.15, 130.46, 127.71, 126.86, 123.02, 121.72, 110.63, 91.27, 86.25, 72.87, 72.48, 70.58, 70.38, 67.23, 37.46, 31.69, 29.17, 29.07, 25.12, 22.64, 14.11; FABMS (in 3-nitrobenzyl alcohol) *m/e* (rel intensity) 1386 (MH^+, 100). Anal. Calcd for $C_{86}H_{92}N_6O_4Fe_2$: C, 74.55; H, 6.69; N, 6.07. Found: C, 75.32; H, 6.82; N, 5.79.

Reference Compound 11. A morpholine (10 mL) solution of **9** (920 mg, 2.1 mmol), **20** (49 mg, 0.20 mmol), $(Ph_3P)_4Pd$ (19 mg, 16 μmol), and CuI (3.6 mg, 19 μmol) was stirred at 110 °C for 5 h. After removal of the solvent, the residue was poured into water and extracted with $CHCl_3$. The $CHCl_3$ extract was evaporated and chromatographed (silica gel; eluent, hexane/CH_2Cl_2 5:1) to give **11**: yield 54% (95 mg); mp 232−234 °C; IR (KBr) 2208 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.31 (s, 4 H), 8.04 (s, 4 H), 4.58 (t, J = 1.8 Hz, 4 H), 4.52 (t, J = 1.8 Hz, 4 H), 4.33 (t, J = 1.8 Hz, 4 H), 4.30 (t, J = 1.8 Hz, 4 H); ^{13}C NMR ($CDCl_3$) δ 131.13, 127.94, 127.55, 123.75, 121.59, 87.50, 76.39, 74.15, 72.18, 70.98, 41.31; FABMS (in 3-nitrobenzyl alcohol) *m/e* (rel intensity) 870 (M^+, 25).

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Supporting Information Available: Copies of ^1H NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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