Induction of Diastereoselectivity in Fe(II) Tris(amino acid−bipyridine) Complexes

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A group of iron(II) tris-bipyridine complexes bearing L-amino acids (L-Lys, L-Phe, L-Ser, L-Val) was prepared to investigate the predetermination of chirality of metal complexes by the chiral amino acid subunits. Noncovalent interactions and solvent polarity seemed to be important factors in inducing diastereoselectivity of the metal complexes. These phenomena were explained by ^{1}H NMR and CD spectroscopic studies and molecular mechanics calculations.

Introduction

Despite the wide potential application of octahedral metal complexes with bipyridine-derived chiral ligands,[1] predetermination of chirality at the metal centers has only recently become a subject of systematic investigation.[2] Mononuclear metal complexes containing more than one bipyridine ligand in cis configuration have two forms of helical chirality (Δ and Λ configuration). Predetermination of chirality in octahedral metal complexes can be reached only through diastereoselective processes. Optically pure complexes can be obtained by incorporating chiral centers into the ligating chains.[3] Relatively less successful chiral predetermination with chiral bidentate bipyridyl ligands has been achieved,[4] whereas many metal complexes showing diastereomeric excess with various multidentate ligands[2] (even diastereomerically pure compounds showing a complete chiral induction)[5] have been reported.

We are interested in generating enantiomerically pure helical tris(bipyridine)-type complexes by diastereoselective complexation with three chiral bidentate bipyridyl ligands, in which chirality comes from L-amino acids attached on the 5 and 5′ positions of 2,2′-bipyridine-5,5′-dicarboxylic acid.[4a,6] This approach exploits nonbonded interactions between peripheral chiral appendages on bidentate chelate units.[7] The factors influencing the chirality induction in the formation of these chiral tris(bipyridine)-type complexes are noncovalent interactions such as hydrogen bonds[8] and van der Waals interactions[9] and the solvation effect.[10] This paper reports the synthesis and Fe(II) complexing behavior of a series of 2,2′-bipyridines substituted with L-amino acid derivatives (L-Lys, L-Phe, L-Ser, and L-Val). Circular dichroism (CD) spectroscopy was used to identify the major compound of the diastereomeric mixture in each complex and the diastereomeric excess was determined by the ^{1}H NMR spectroscopy. In addition, the roles of the amino acid side chains and solvents in the diastereomeric complex formation are discussed.

Results and Discussion

Syntheses of Ligands and Complexes. The syntheses of ligands (**3**, **4**, **5**, and **6**) and metal complexes (**7**, **8**, **9**, and **10**) are outlined in Scheme 1. **1** and **2** were prepared according to a reported procedure.[11] Ligands (**3**, **4**, **5**, and **6**) were synthesized by adding DIEA (diisopropylethylamine) and acid-protected L-amino acid derivatives to a solution of **2** in methylene chloride. Fe(II) complexes were prepared by mixing iron(II) chloride tetrahydrate and each ligand (**3**, **4**, **5**, and **6**) in 5% methylene chloride/methanol solution as previously described.[10b]

Determination of Diastereomeric Excess (de). The ^{1}H NMR spectra of the Fe(II) tris(amino acid−bipyridine) were used to determine the relative ratio between the major and minor isomers using peak intensities,[5b,6,12] but they cannot be used to deduce absolute structural information. Each of the Fe(II) tris(amino acid−bipyridine) was examined by CD spectroscopy to determine the absolute configuration of the major coordination isomer in solution.[13] Since the sign of the CD bands in the 300−

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Scheme 1

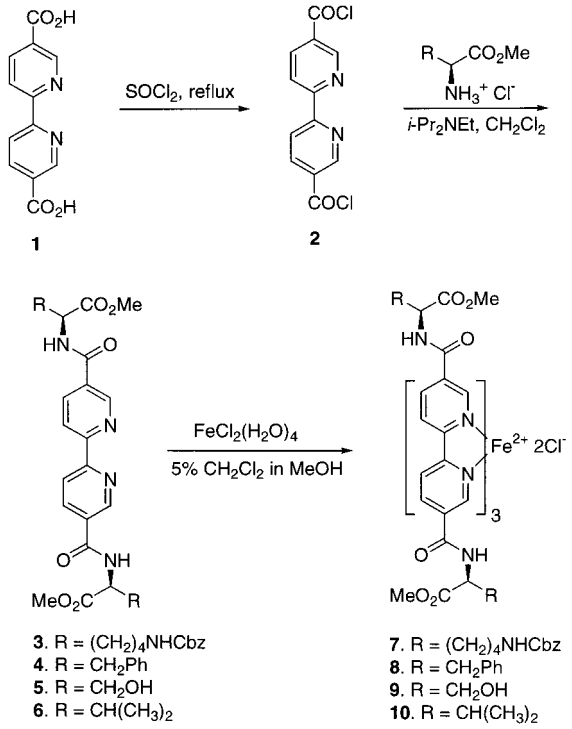

Table 1. Determination of Configurations and de's by CD and ^{1}H NMR

	CD (sign and configuration)[a]		NMR (de, %)[b]	
	acetone	methanol	acetone	methanol
7	−(Δ)[c]	0	−80	−1
8	0	−(Δ)	0	−48
9	+(Λ)	+(Λ)	71	32
10	−(Δ)	+(Λ)	−47	24

[a] The major isomers were identified by the CD sign in the 300−340 nm range.[13] [b] The de's were determined by comparing the peak intensities of the 6-Py-H proton or chiral methine proton in the ^{1}H NMR spectrum; de = % of Λ isomer − % of Δ isomer. [c] The minus (−) sign indicates that the configuration of the major isomer is Δ.

340 nm range is known to be due to chirality at the metal center, the absolute configurations of the major isomers of the Fe(II) complexes in solution can be deduced by comparison of their CD spectra with the reported CD data of Fe(II)(bipyridine)$_3$ in that region.[4,6,13] The results are summarized in Table 1.

All Fe(II) complexes were equilibrated between the major and minor isomers in each solvent by storage for 5 days before CD and NMR measurements were performed. It emerged that about 2 days were required to reach equilibrium for each solvent (Figure 1). The major isomers were identified in each solvent by the CD sign in the 300−340 nm range[4,6,13] (Figures 2 and 3), and the relative abundance of the diastereomeric coordination isomers in each solvent was determined by comparing the peak intensities of the 6-Py-H proton or chiral methine proton in the ^{1}H NMR spectrum (Figure 4); the results are also summarized in Table 1.

The CD signals also appear in the metal-to-ligand charge-transfer region of the Fe(II) complexes (Figure 3), showing positive bands at around 583 nm. This implies that the Fe(II) tris(amino acid−bipyridine) complexes are formed. Sasaki and co-workers showed that a strong denaturant (6 M guanidine hydrochloride) completely

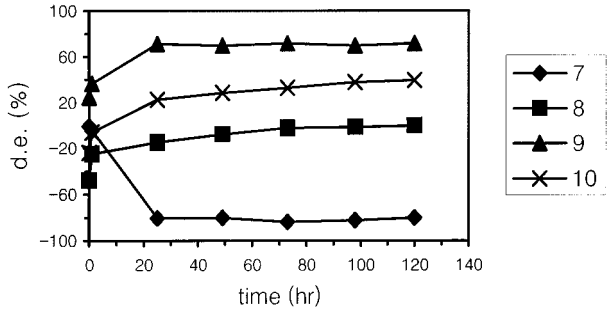

Figure 1. Time-dependent isomerization of the Fe(II) complexes in acetone-d_6 at 300 K. The minus sign means that Δ isomer is the major isomer.

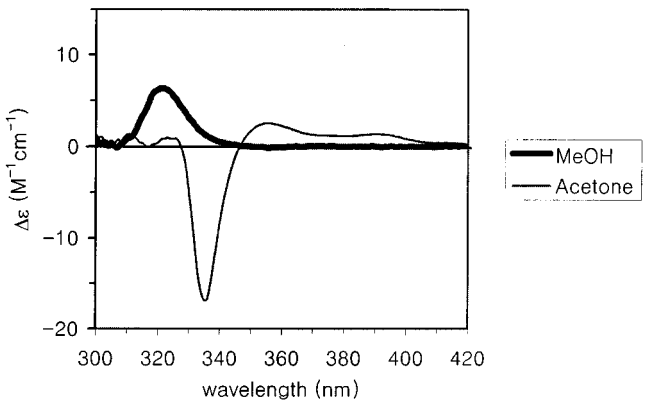

Figure 2. Circular dichroism spectra of **10** in methanol and acetone at 300 K.

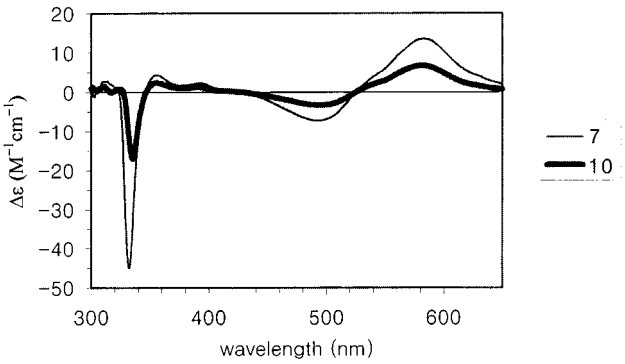

Figure 3. Circular dichroism spectra of **7** and **10** in acetone at 300 K.

removed the CD bands of Fe(II)(peptide−bipyridine)$_3$ between 300 and 350 nm, which indicated that the folded protein structure rather than the mere proximity of L-amino acids appended on bipyridine should be responsible for the chirality induction at the metal center.[4a] However, our results suggest that noncovalent intra- and/or interligand interactions between L-amino acid units should result in the induction of a de in each complex.

As shown in Table 1, not only the intra- and/or interligand interactions but also solvation effects should play important roles in the determination of de's and major isomers. Compounds **7** and **9**, which contain hydrogen bond donors and acceptors in the side chains of the amino acid units, showed a higher de in acetone than in methanol which precludes the formation of hydrogen bonds. Since hydrogen bonds between L-amino acid moieties are dependent on the polarity of a solvent,

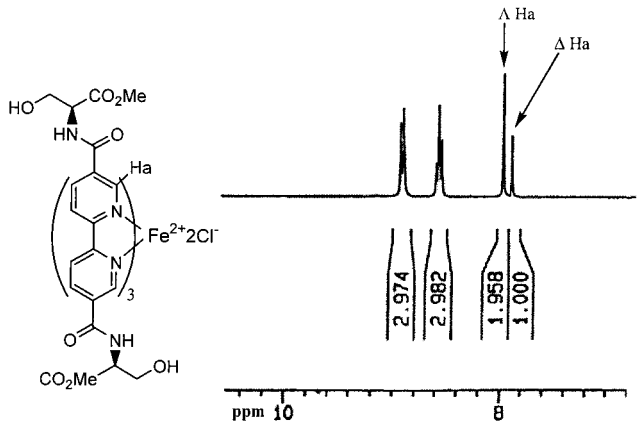

Figure 4. ^{1}H NMR spectrum of **9** in acetone-d_6 at 300 K.

solvents should play an important role in the predetermination of chirality at the metal center. Difficulty in forming hydrogen bonds due to the nonpolar side chains of L-amino acid units of **8** and **10** presumably resulted in lower de's compared to **7** and **9**. van der Waals interactions between the nonpolar side chains of L-amino acid units of **8** and **10** may be responsible for the different extent of induction of de's in **8** and **10**. However, there exist possible explanations for the influence of hydrogen bonds on the predetermination of chirality of **7** and **9**. A cosolvent system (acetone/methanol, v/v, 1:1) was used to investigate the role of the solvent and the participation of hydrogen bonds in the chirality induction. **7** and **9** in that solvent system exhibited values of de between those for acetone and methanol. (**7**, −45%; **9**, 47%). This result shows that hydrogen bonds dependent on the solvent polarity play an important role in inducing de. Therefore, we believe that the hydrogen bonding interaction and/or van der Waal interactions and the solvation effect should play a cooperative role in the determination of de. Consequently, this result indicates that the chiral induction of Fe(II) trischelate complexes by amino acid groups is effective.

We have investigated the structural origin of the induced diastereoselectivity of **9** by molecular modeling studies. The X-ray crystal structure of Fe(II) tris-bipyridine was retrieved from the Cambridge Crystallographic Database and used as a starting point for molecular mechanics calculations.[14] Six L-Ser methyl esters were attached on the 5 and 5′ positions of bipyridine ligands through amide bonds (see **9** of Scheme 1). Conformational searches on Δ and Λ complexes of **9** were carried out using the MacroModel[15] implementation of the Amber force field and constraining the Fe(II) tris-bipyridine core to the X-ray structure geometry. The energy difference of the two diastereomers seems to originate from the different numbers of H-bonds and van der Waals repulsive interactions between intra- and/or interligand amino acid side chains. Figure 5 showed that the lowest energy conformation of the Λ isomer (−925.3 kJ/mol) has 6 intraligand hydrogen bonds and that of the Δ isomer (−849.1 kJ/mol) has 4 intraligand hydrogen bonds and 1 interligand hydrogen bond. The diastereoselectivity of **9** probably does not arise from favorable hydrogen bonding interactions within the Λ isomer formed to a greater extent but rather through destabilization of the Δ isomer formed to a lesser extent. Though the structures shown in Figure 5 may not be the optimal conformations, they show representative conformations populated to a significant extent.

Conclusion. We have prepared a group of Fe(II) tris-bipyridine complexes bearing L-amino acids (L-Lys, L-Phe, L-Ser, L-Val) to investigate the induction of diastereoselectivity of metal complexes by the chiral amino acid subunits. Noncovalent interactions such as hydrogen bonding, steric interactions, and the solvation effect seemed to be important factors in determining the diastereoselectivity of the metal complexes. These phe-

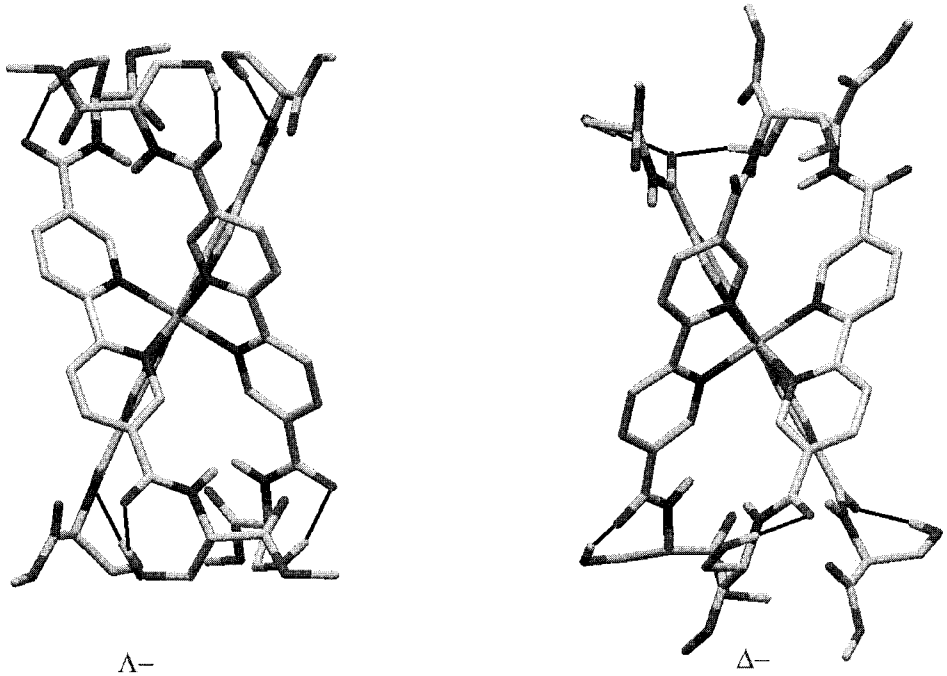

Figure 5. The lowest-energy conformations of Λ-**9** (left) and Δ-**9** (right). Hydrogens except NH and OH have been omitted for clarity.

nomena were explained by ^{1}H NMR and CD spectroscopic studies and molecular mechanics calculations.

Experimental Section

All reagents were used as received without further purification. All solvents were purified by known standard procedures. **1** was prepared according to a literature procedure.[11] NMR spectra were recorded at 300 MHz (^{1}H) and 75 MHz (^{13}C) using a Bruker AMX-300 spectrometer. Chemical shift values are reported in ppm using known chemical shift values of residual nondeuterated solvent peaks as a reference. CD spectra were collected on a JASCO J-720 spectropolarimeter. Elemental analyses were performed by the Inter-University center for Natural Science Research Facilities at Seoul National University.

General Procedure for the Ligand Syntheses. Thionyl chloride (10 mL) was added to 100 mg (0.41 mmol) of 5,5′-dicarboxy-2,2′-bipyridyl with stirring and was refluxed for 3 h. After cooling the reaction mixture, excess thionyl chloride was removed in vacuo to give the diacid chloride which was used without further purification. To a solution of the above diacid chloride and DIEA (1 mL) in methylene chloride was added C-protected L-amino acid methyl ester hydrochloride (1.6 mmol), and the mixture was stirred at room temperature for 18 h. The reaction mixture was washed with a saturated aqueous $NaHCO_3$ solution and with brine. Solvent removal followed by trituration with diethyl ether afforded the desired product as an amorphous solid. The white solid was further purified by column chromatography or recrystallization.

General Procedure for the Iron(II) Complex Syntheses. A third equivalent of iron(II) chloride tetrahydrate was mixed with each ligand in 5% CH_2Cl_2/methanol. The solvent was removed to give the corresponding iron(II) complex in quantitative yield.

5,5′-Di-L-Lys-2,2′-bipyridine (3) and Iron(II)tris(5,5′-di-L-Lys-2,2′-bipyridyl) Dichloride (7). Purification by column chromatography (CH_3OH/CH_2Cl_2 1:20 to 1:10) and recrystallization ($CH_3OH/CH_2Cl_2/Et_2O$ 20:1:5) afforded 80 mg (25%) of **3** as a white solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.42 (8H, m, $-CH_2CH_2-$), 1.83 (4H, m, $-EtCH_2CHN-$), 2.99 (4H, m, $-EtCH_2CHN-$), 3.66 (6H, s, CO_2CH_3), 4.44 (2H, t, J = 14.6 Hz, $-CHN-$), 4.98 (4H, s, $PhCH_2$), 7.34 (10H, m, Ph*H*), 8.42 (2H, d, J = 10.5 Hz, 3-py*H*), 8.54 (2H, d, J = 8.1 Hz, 4-py*H*), 9.16 (2H, s, 6-py*H*); ^{13}C NMR (75 MHz, DMSO-d_6) δ 23.8, 29.8, 31.0, 52.8, 53.5, 53.6, 65.9, 128.5, 129.2, 130.5, 137.5, 138.1, 149.6, 156.9, 157.3, 165.7, 173.4. Anal. Calcd for $C_{42}H_{48}N_6O_{10}$: C, 63.30; H, 6.07; N, 10.55. Found: C, 63.26; H, 5.81; N, 10.52.

7 was prepared by the general procedure: UV/vis (CH_2Cl_2) λ_{max} (ϵ, M^{-1} cm^{-1}) = 307 (49438), 562 nm (4594); MS (ES^+) m/z 1222.9 ($[M - 2Cl^-]^{2+}$, 100%). Anal. Calcd for $C_{126}H_{144}F_{12}FeN_{18}O_{30}P_2$ (counter anion Cl^- was replaced with PF_6^-): C, 55.30; H, 5.30; N, 9.21. Found: C, 54.96; H, 5.42; N, 8.92.

5,5′-Di-L-Phe-2,2′-bipyridine (4) and Iron(II)tris(5,5′-di-L-Phe-2,2′-bipyridyl) Dichloride (8). Purification by column chromatography (CH_3OH/CH_2Cl_2 1:20) afforded 130 mg (56%) of **4** as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.23 (4H, dd, J_1 = 24.6 Hz, J_2 = 14.1 Hz, $PhCH_2$), 3.74 (6H, s, $COCH_3$), 5.05 (2H, dd, J_1 = 13 Hz, J_2 = 5.6 Hz, $-NCHCO_2-$), 6.64 (2H, d, J = 7.5 Hz, $-NHCO-$), 7,19 (10H, m, Ph*H*), 8.10 (2H, d, J = 8.1 Hz, 3-py*H*), 8.46 (2H, d, J = 8.4 Hz,4-py*H*), 8.94 (2H, s, 6-py*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.12, 53.0, 54.0, 121.5, 127.8, 129.2, 129.7, 130.0, 136.1, 136.3, 148.3, 157.7, 165.5, 172.3. Anal. Calcd for $C_{32}H_{30}N_4O_6$: C, 67.83; H, 5.34; N, 9.89. Found: C, 66.66; H, 5.34; N, 9.91.

8 was prepared by the general procedure: UV/vis (CH_2Cl_2) λ_{max} (ϵ, M^{-1} cm^{-1}) = 308 (91253), 562 nm (5646); MS (ES^+) m/z 1791.1 ($[M - Cl^-]^+$, 7%), 878.0 ($[M - 2Cl^-]^{2+}$, 100%). Anal. Calcd for $C_{96}H_{90}N_{12}O_{18}FeCl_2$: C, 63.13; H, 4.97; N, 9.20. Found: C, 63.31; H, 5.01; N, 9.05.

5,5′-Di-L-Ser-2,2′-bipyridine (5) and Iron(II)tris(5,5′-di-L-Ser-2,2′-bipyridyl) Dichloride (9). Purification by column chromatography (CH_3OH/CH_2Cl_2 1:10) and recrystallization (CH_2Cl_2) afforded 136 mg (74%) of **5** as a white solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.67 (6H, s, CO_2CH_3), 3.83 (4H, d, J = 5.4 Hz, CH_2OH), 4.59 (2H, dd, J_1 = 15.5 Hz, J_2 = 5.4 Hz, $-NCHCO_2-$), 5.13 (2H, t, J = 6.0 Hz, O*H*), 8.42 (2H, d, J = 8.3 Hz, 3-py*H*), 8.55 (2H, d, J = 8.4 Hz, 4-py*H*) 9.01 (2H, d, J = 7.5 Hz, N*H*CO−), 9.17 (2H, s, 6-py*H*); ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.7, 165.7, 157.4, 149.6, 137.5, 130.5, 121.5, 61.7, 56.5, 52.8; MS (FAB^+) m/z 447 $[M + H]^+$. Anal. Calcd for $C_{20}H_{22}N_4O_8$: C, 53.81; H, 4.97; N, 12.55. Found: C, 54.08; H, 5.01; N, 12.54.

9 was prepared by the general procedure: UV/vis (CH_2Cl_2) λ_{max} (ϵ, M^{-1} cm^{-1}) = 308 (31908), 569 nm (2639); MS (ES^+) m/z 1430.5 ($[M - Cl^-]^+$, 1%), 697.5 ($[M - 2Cl^-]^{2+}$, 100%). Anal. Calcd for $C_{60}H_{66}Cl_2FeN_{12}O_{24}\cdot 3H_2O$: C, 47.41; H, 4.77; N, 11.06. Found: C, 47.42; H, 4.81; N, 11.04.

5,5′-Di-L-Val-2,2′-bipyridine (6) and Iron(II)tris(5,5′-di-L-Val-2,2′-bipyridyl) Dichloride (10). Purification by column chromatography (CH_3OH/CH_2Cl_2 1:20) afforded 136 mg (71%) of **6** as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (12H, m, $(CH_3)_2C$), 2.32 (2H, dd, J_1 = 11.7 Hz, J_2 = 6.9 Hz, Me_2CH), 3.81 (6H, s, CO_2CH_3), 4.82 (2H, dd, J_1 = 8.4 Hz, J_2 = 4.8 Hz, $-NCHCO-$), 6.70 (2H, d, J = 8.1 Hz, $-NHCO-$), 8.25 (2H, d, J = 7.5 Hz, 3-py*H*), 8.59 (2H, d, J = 8.4 Hz, 4-py*H*), 9.12 (2H, s, 6-py*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.5, 19.4, 31.9, 52.8, 58.1, 121.4, 130.2, 136.3, 148.4, 157.6, 165.9, 172.8. Anal. Calcd for $C_{24}H_{30}N_4O_6$: C, 61.26; H, 6.43; N, 11.91. Found: C, 61.35; H, 6.50; N, 12.00.

10 was prepared by the general procedure: UV/vis (CH_2Cl_2) λ_{max} (ϵ, M^{-1} cm^{-1}) = 311 (62544), 565 nm (8738); MS (ES^+) m/z 1502.6 ($[M - Cl^-]^+$; 10%), 733.7 ($[M - 2Cl^-]^{2+}$; 80%). Anal. Calcd for $C_{72}H_{90}Cl_2FeN_{12}O_{18}$: C, 56.22; H, 5.90, N, 10.93. Found: C, 55.91; H, 6.01; N, 10.79.

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