The Preparation of Protoheme Mono-*N*-[5-(2-methyl-1-imidazolyl)pentyl]amide and Its Oxygenation

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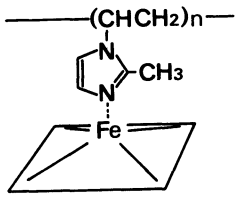
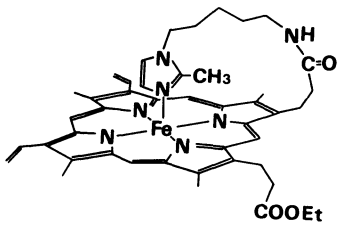
Iron(II)protoporphyrin IX *N*-[5-(2-methyl-1-imidazolyl)pentyl]amide ethyl ester (**1**) and its derivatives (**2**—**4**) were prepared. They predominantly form pentacoordinate heme complexes in organic and aqueous solutions, based on their 2-methylimidazole-ligand and spacer *N*-pentylamide groups. Oxygen adducts of **1**—**4** were rapidly formed on exposure to oxygen in *N*,*N*-dimethylformamide (DMF) at −30 °C, and their life-times were more than 30 min.

It is interesting to attempt to synthesize an iron–porphyrin complex with an oxygen-binding ability. Much recent work has been reported on such attempts, and two approaches have been partially successful. The first is the elegant steric modification of porphyrin: porphyrins have been replaced with "picket fence groups,"[1] "crown ether groups,"[2] "strap groups,"[3] *etc.*[4,5] The second approach is to attach the iron–porphyrin complex to a polymer chain.[6-8] By these means, a reversible oxygen bnding has been achieved in aprotic solvents or in the solid state, but in an aqueous medium all the iron–porphyrin derivatives have been irreversibly oxidized.



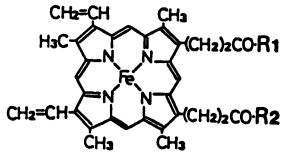
Scheme 1.

Recently, the present authors have found that the heme (iron(II)–protoporphyrin IX) complex with poly-(1-vinyl-2-methylimidazole) (PMI) (Scheme 1) forms the oxygen adduct even in an aqueous solution at −30 °C.[9] It is very important for oxygen binding in an aqueous solution that the heme complex has pentacoordinate structure the sixth coordination site of which is vacant to bind oxygen.[10]

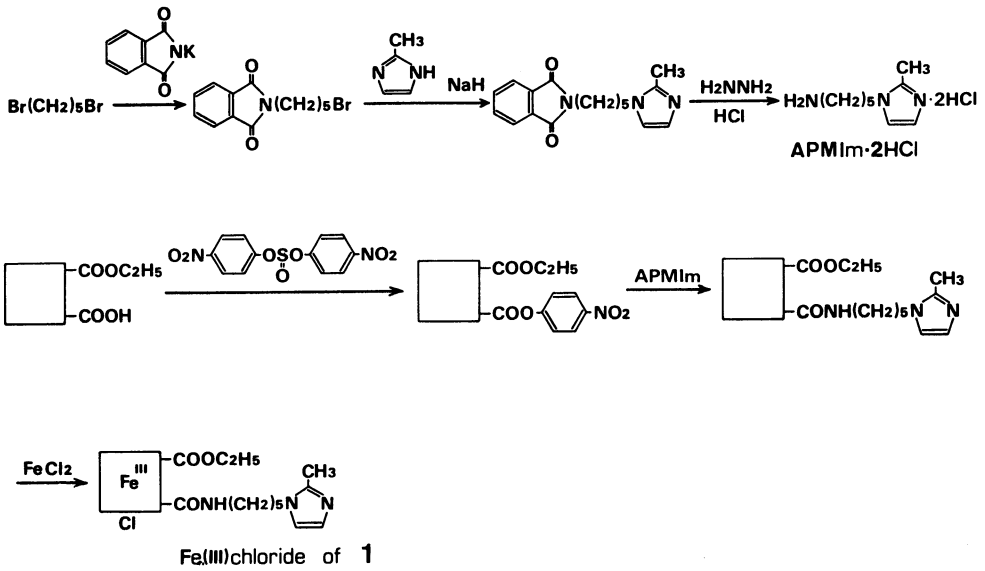


Scheme 2.

In this work, we synthesized heme derivatives having a 2-methylimidazole-ligand with *N*-pentylamide groups, **1**—**4**, which are expected to preferentially form the pentacoordinate heme complexes, as is shown in Scheme 2. A series of heme derivatives with covalently bound imidazole-ligands has already been studied by Traylor.[11-13] The mesoheme *N*-[3-(1-imidazolyl)propyl]amide ethyl ester derivative (**6**) is typical and forms the oxygen adduct in an aprotic, organic solvent.[12] However, the solution of **6** gave the visible spectrum of hexacoordinate heme, the sixth ligand having been derived from the solvent, and was irreversibly oxidized in aqueous media. On the other hand, the heme derivative with the 2-methylimidazole-ligand with an *N*-propylamide group has also been reported. However, the 2-methylimidazole-ligand could not coordinate to the central iron-ion because the *N*-propylamide group was too short, and the tetracoordinate heme complex was predominantly formed. From these results and the geometrical consideration of heme derivatives shown in Scheme 2, we selected the *N*-pentylamide group as a spacer group which bonds the 2-methylimidazole-ligand with heme and synthesized **1** and their derivatives: **2** as a water-soluble derivative, **3** as a bis(ligand)-type derivative, and **4** as a polymer-bound derivative. The coordination structure and oxygen binding ability of these heme derivatives (**1**—**4**)



Compound	R_1	R_2
Heme	OH	OH
1	$NH(CH_2)_5$ (2-methylimidazolyl)	OC_2H_5
2	$NH(CH_2)_5$ (2-methylimidazolyl)	OH
3	$NH(CH_2)_5$ (2-methylimidazolyl)	$NH(CH_2)_5$ (2-methylimidazolyl)
4	$NH(CH_2)_5$ (2-methylimidazolyl)	Gly-PEG
5	$NH(CH_2)_3$ (2-methylimidazolyl)	OC_2H_5
6	$NH(CH_2)_3$ (2-methylimidazolyl)	OC_2H_5
7	$NH(CH_2)_3$ (imidazolyl)	$NH(CH_2)_3$ (imidazolyl)



Scheme 3.

were studied in comparison with those of the previously reported Traylor's heme derivatives (**5**, **6**, and **7**) and with those of the polymer-heme complexes.

Results and Discussion

1 was obtained by the reaction of 1-(5-aminopentyl)-2-methylimidazole and the protoporphyrin IX monoethyl ester. The reaction process is illustrated in Scheme 3. **2** was obtained by hydrolyzing **1**. **3** was similarly prepared from 1-(5-aminopentyl)-2-methylimidazole and protoporphyrin IX, while **4** was obtained from **2** and poly(ethylene glycol)glycine[14] by using dicyclohexylcarbodiimide. The analytical data are given in the Experimental section.

The ultraviolet and visible absorption spectra of **1**, **5**, and **6** in the DMF solution (volume ratio DMF/H_2O= 9/1) are shown in Fig. 1. The visible spectrum of **1** was characterized by a single-peak absorption at 557 nm, the coordination structure of which was assigned to the pentacoordinate one; the iron(II) ion was in a high-spin state like myoglobin (557 nm). The molar absorption coefficients (ε) of **1** were 2.3×10^5 at 433 nm and 1.4×10^4 at 557 nm, nearly equal to those of the pentacoordinate heme complex with a large excess of 2-methylimidazole. On the other hand, the spectrum of **5** was broadened considerably, much like that of the tetracoordinate heme complex. This means that the 2-methylimidazole-ligand could not coordinate sufficiently to the central iron(II) ion, probably because of its shorter spacer group (*N*-propylamide group), and the pentacoordinate structure was not completed. **6** showed a double-peak absorption in the visible region (530 and 560 nm, Fig. 1) assigned to the hexacoordinate and low-spin heme complex, as had been reported by Traylor.[11] Although **6** formally has one imidazole-ligand, it forms the hexacoordinate heme complex in solution. The solvent molecule combines with the sixth coordination site of heme.[11] From these results, it may be concluded that **1** more predominantly forms the pentacoordinate heme complex than **5** and **6** do.

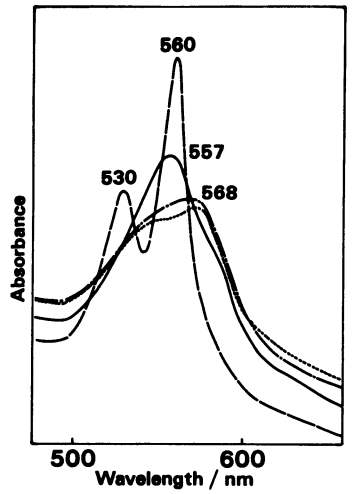


Fig. 1. Visible spectra of the deoxy heme complexes in DMF–H_2O(9/1) at −30 °C.
[Fe(II)]=0.1 mmol dm^{-3}, ——: **1**, —·—: **5**, -----: **6**, ·····: heme.

2 and **3** in aqueous solutions also showed the single-peak absorption at 557 nm, and the pentacoordinate structure was stable in the concentration range from about 0.01 to 10 mmol dm^{-3}. The visible spectrum of **3**, with two 2-methylimidazole-ligands, was identical to that of **1**. This means that one of the 2-methylimidazole pair coordinates to the central iron ion, while the other 2-methylimidazole-ligand can not coordinate to the sixth coordination site of heme. This behavior was like that of 2-methylimidazole-heme which took the pentacoordinate structure even if a large excess of 2-methylimidazole existed. This result was in contrast to that for **7**, which took the very stable hexacoordinate structure.

The oxygenation ability of each complex was measured in DMF–H_2O(9/1) at −30 °C. Except for **7**, all the heme complexes gave the oxygen adduct. As an

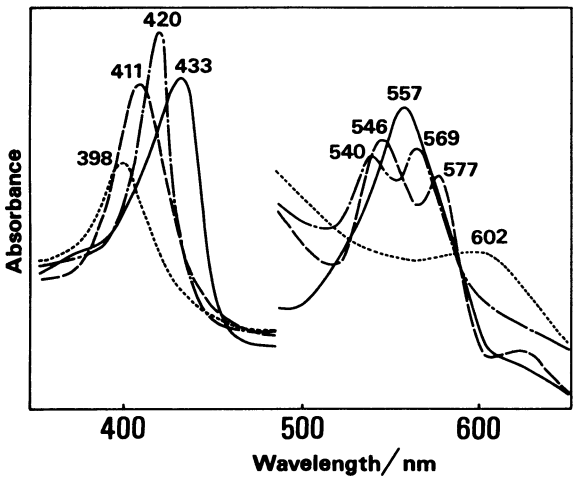


Fig. 2. Ultraviolet and visible spectra of **1** in DMF–H_2O(9/1) at −30 °C.
[**1**]=0.1 mmol dm^{-3}, ——: deoxy complex, ------: O_2-adduct, —·—: CO-adduct, ·····: oxidized complex.

example, the spectrum of the oxy-**1** complex (Fig. 2) was identified as that of the oxygen adduct by means of the following results: (i) The spectrum changed to that of the heme-CO complex when carbon monoxide was bubbled through the solution, and (ii) returned to the deoxy complex when nitrogen gas was introduced.

One must pay careful attention to the residue of the sodium dithionite which is used to prepare the heme complex (see Experimental section), because it often complicates the spectrum of the heme complex under aerobic conditions. The contribution of sodium dithionite and its residue to this reversible oxygenation was denied by the following results: (i) A small excess of sodium dithionite was used for reduction, and no trace of it remained before the oxygen exposure. (ii) The porphyrin ring of heme was degrated, and no oxygenation was observed in the presence of a large excess of dithionite. (iii) Organic reductants, such as L-ascorbic acid or D-glucose, were also effective reducing agents in forming an oxygen complex.

1—**4**, which took the pentacoordinate deoxy structure, immediately bound oxygen. Figure 3(a) shows the isosbestic spectral change in **1** after exposure to oxygen. In contrast, **6** reacted slowly with oxygen, while **7** did not react at all. It may be concluded from these results that the rate of the oxygenation reaction of the pentacoordinate heme complex is high, for the sixth coordination site, *i.e.*, the oxygen-binding site, is vacant.

The oxygen adduct of heme derivatives degraded to form a high-spin hemin complex (weak absorption at about 602 nm) through isosbestic points (528, 590 nm) as is shown in Fig. 4. The degradation obeyed first-order kinetics, and the life-time of the oxygen adduct was calculated by means of the following equation: $1/\tau=(1/t)\ln[(A_0-A_\infty)/(A_t-A_\infty)]$, where τ indicates the life-time of the oxygen adduct and where A_0, A_t, and A_∞ are the absorbance of the visible spectrum of heme-oxygen adduct at the beginning, at after time t, and when the degradation is complete respectively. The life-time is summarized in Table 1.

Table 1. Life-times of the oxygen adducts at −30 °C

Complex	Life-time/min	
	In DMF–H_2O (9/1)	In H_2O–ethylene glycol (1/1)
PMI-heme[a)]	63	25
1	32	—
2	—	Oxidized
3	72	1
4	35	Oxidized
2-Methylimidazole-heme[b)]	6	Oxidized
6	98	Oxidized
7	Oxidized	Oxidized

a) [2-Methylimidazole residue]/[heme]=500. b)[2-Methylimidazole]/[heme]=5000.

The life-time of oxy-**1** was much longer than that of the 2-methylimidazole-heme system; **1** could give oxygen adduct with not only a large formation rate, but also a long life-time. Table 1 shows that **3** and PMI-

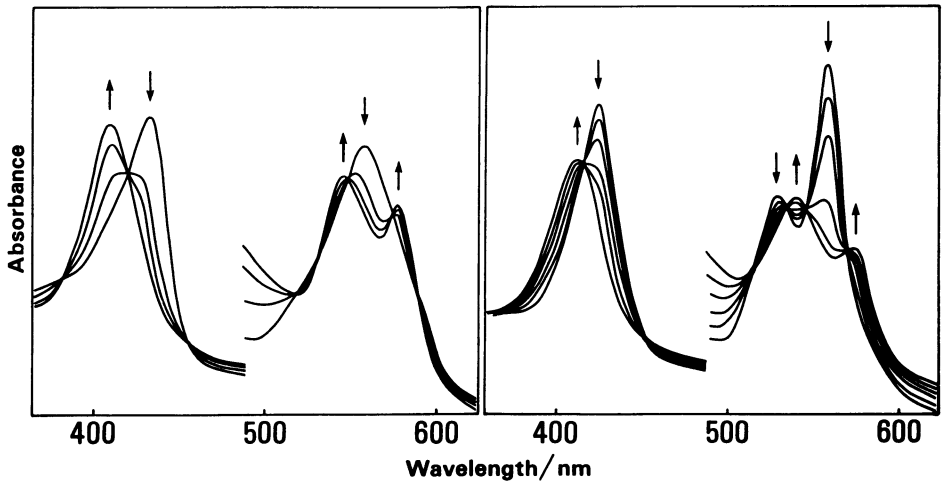


Fig. 3. Oxygenation of **1** (a) and **6** (b) in DMF–H_2O(9/1) at −30 °C. After exposing to oxygen: 0, 0.5, 1, and 2 min for (a); 0, 1, 2, 5, 10, and 15 min for (b).

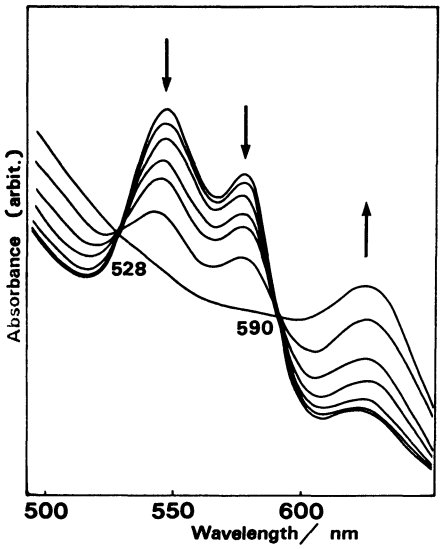


Fig. 4. Degradation of the oxygen adduct of **1** in DMF–H_2O(9/1) at −30°C. After 0, 5, 10, 20, 30, 60 min, and 1 d.

heme form more stable oxygen adducts, which approach the oxy-**6** studied by Traylor. 2-Methylimidazole residue that exists near the sixth coordination site of heme makes a good contribution to the stabilization of the oxygen adduct.

The oxygenation reaction was also checked in H_2O–ethylene glycol (1/1) at −30 °C. PMI-heme and **3**, which gave stable oxygen adducts in DMF–H_2O (9/1), could also form oxygen adducts even in an aqueous medium, though they were not so stable. The reasons for the oxygen-binding ability of PMI-heme and **3** in an aqueous medium are presumed to be as follows: (i) PMI-heme and **3** form pentacoordinate, high-spin-state complexes with large formation constants, and the rates of oxygenation are high, and (ii) the polymer-ligand, PMI, or the unchelated 2-methylimidazole sterically occludes heme and provides an effective hydrophobic environment which surrounds the oxygen adduct.

The synthesis and oxygen-binding ability of polymer-bound **1** will be presented in a subsequent paper.

Experimental

*Synthesis of Iron(III)protoporphyrin IX Mono-*N*-[5-(2-methyl-1-imidazolyl)pentyl]amide Ethyl Ester Chloride (Iron(III) Chloride of 1) and the Corresponding Amide Acid (Iron(III) Chloride of 2).* 1-(5-Aminopentyl)-2-methylimidazole (AMPIm) was prepared by a Gabriel reaction. Potassium phthalimide (74 g, 0.4 mol) was suspended in 1,5-dibromopentane (300 g, 1.3 mol), after which the mixture was allowed to react at 190—200 °C for 12 h. The mixture was steam-distilled to remove the unreacted 1,5-dibromopentane. *N*-(5-Bromopentyl)phthalimide (BPP) was extracted with chloroform, dried (Na_2SO_4), evaporated to dryness, and then recrystallized from ethanol; pale yellow crystals (yield, 59.8 g).

50% oily sodium hydride (4.80 g) was suspended in dry toluene (100 ml). 2-Methylimidazole (8.21 g, 0.10 mol) was added to this suspension, and the mixture was refluxed for 5 h under nitrogen. Then, BPP (29.6 g, 0.10 mol) was added, and the mixture was allowed to react for 15 h under reflux. After filtration, the solution was evaporated to dryness. The brown oily product was chromatographed on a silica-gel column (about 300 mesh, 5 cm × 45 cm for operating 1.5 g). The fourth fraction with chloroform–methanol (20 : 1) was collected (R_f=0.19 with chloroform–methanol (20 : 1)) and evaporated to dryness. *N*-(5-Phthalimidopentyl)-2-methylimidazole (PPIm): pale yellow powder; yield, 17.8 g (59.9%), IR; ν_{ring} 1621 (phenyl), 1620 (imidazole), $\nu_{C=O}$ 1780, 1720 cm^{-1}. Found: C, 69.1; H, 6.58; N, 13.9%. Calcd for $C_{17}H_{19}N_3O_2$: C, 68.7; H, 6.40; N, 14.1%.

PPIm (17.7 g, 59.5 mol) was dissolved in methanol (250 ml). Hydrazine monohydrate (2.98 g, 59.5 mol) was added to this solution, which was then refluxed for 15 h. Then water (200 ml) was added, and the methanol was removed by evaporation. Concd hydrochloric acid (200 ml) was added to this aqueous solution, and the mixture was refluxed for 2 h. After cooling to 0 °C, the white precipitate was filtered off. The filtrate was evaporated to dryness, and the crude product was recrystallized from ethanol. 1-(5-aminopentyl)-2-methylimidazole dihydrochloride (APMIm 2HCl): pale yellow crystals; yield 12.1 g (84.7%) ^1H NMR (DMSO-d_6, δ): imidazole C–H, 7.5, 7.7(2H); $-(CH_2)_5-$, 1.3—1.8(6H), 2.7(2H), 4.1(2H); $-CH_3$, 2.6(3H); $-NH_3^+$, 8.2(3H). Found: C, 45.1; H, 7.88; N, 17.4; Cl, 29.6%. Calcd for $C_9H_{19}N_3Cl_2$: C, 45.0; H, 7.92; N, 17.5; Cl, 29.6%. IR: ν_{ring} 1605 (imidazole), $\nu_{NH_3^+}$ 3000, 2510, 2420 cm^{-1}.

On the other hand, the protoporphyrin IX monoethyl ester (PMEE) was prepared as follows. Protoporphyrin IX sodium salt (4.5 g, 7.4 mmol) and phosphorus pentachloride (2.4 g, 11.5 mmol) were dissolved in chloroform (250 ml), and the mixture was stirred for 30 min at 30 °C. Ethanol (15 ml) was added, and this mixture was stirred for 30 min, after which more ethanol (15 ml) was added. The reaction was conveniently followed by examining the TLC (silica-gel, chloroform–methanol (10 : 1)). The amount of the second fraction, based on PMEE, increased as the esterification proceeded. The reaction was finished after 45 min, and chloroform (200 ml) and water (1.5 ml) were added to this solution. The pH was then controlled to 6.0 by adding triethylamine. After washing with water, the chloroform layer was filtered and concentrated. The crude product was chromatographed on a silica-gel column (5 cm × 20 cm for operating 2 g). The column was eluted with chloroform until the eluent was very pale. The PMEE was obtained with chloroform–methanol (15 : 1) as the first fraction; 30% yield.

Protoporphyrin IX mono-*N*-[5-(2-methyl-1-imidazolyl)-pentyl]amide ethyl ester (PMImPe) was synthesized as follows. PMEE (2.7 g, 4.5 mmol) was dissolved in a mixture of DMF (30 ml) and pyridine (30 ml), after which bis(*p*-nitrophenyl) sulfite (5.9 g, 18 mmol) was added . After stirring for 18 h at room temperature, the solution was concentrated by evaporation. The residue was dissolved in chloroform, and the insoluble part was removed by filtration. After concentration, PMImPe was precipitated from diethyl ether–petroleum ether (1 : 1). The brown, powdered product was chromatographed on a silica-gel column (4 cm × 20 cm for operating 1 g) eluted with benzene–acetone (25 : 1). The *p*-nitrophenyl ester was obtained as the main fraction in a 65.9% yield.

The *p*-nitrophenyl ester (0.85 g, 1.2 mmol) and PMEE (0.25 g, 1.5 mmol) were dissolved in chloroform (30 ml), and the mixture was stirred for 1 d at room temperature. After concentration, the residue was dissolved in chloroform, and the mixture was filtered. Then PMImPe was precipitated

from diethyl ether. PMImPe: brown powder; yield, 733 mg (83.6%). IR: $\nu_{C=O}$ 1640, 1550 (amide), 1730 (ester). Found: C, 73.1; H, 7.21; N, 13.2%. Calcd for $C_{45}H_{53}N_7O_3$; C, 73.1; H, 7.17; N, 13.3%. ^{1}H NMR ($CDCl_3$, δ): ring $-CH_3$, 3.55—3.80(12H); imidazole $-CH_3$, 0.30(3H), imidazole $-H$, 4.7(1H) propionic α-CH_2, 4.10(4H); propionic β-CH_2, 3.15 (4H); α-CH_2, 0.90(2H); β-CH_2, 0.20(2H); γ-CH_2, 2.35(2H); δ-CH_2, 1.95(2H); ε-CH_2, 2.83(2H); NH, 5.8(1H); *meso*-H, 9.6—9.9(4H); vinyl-H, 5.0—5.5, 6.9(3H); OC_2H_5, 4.10(2H), 2.05(3H); pyrrole-H, 4.50(2H).

By the incorporation of the iron ion in PMImPe, iron(III)-protoporphyrin IX mono-*N*-[5-(2-methyl-1-imidazolyl)pentyl]amide ethyl ester chloride (iron(III) chloride of **1**) was obtained. PMImPe (300 mg, 0.36 mmol) was dissolved in DMF (300 ml). $FeCl_2 \cdot nH_2O$ (180 mg) was added to this solution, and the mixture was heated to 70 °C under nitrogen for 1 h. The solvent was removed by evaporation, and the residue was extracted with a chloroform–methanol (3 : 1) mixture. The crude product was chromatographed on a basic alumina column (3 cm × 15 cm), eluted with chloroform–methanol (30 : 1). The first and second fractions (iron(III) chloride and μ-oxo dimer of **1**) were collected and brought to dryness. Iron(III) chloride of **1**: brown powder; yield, 172 mg (51.2%). Found: C, 65.1; H, 6.10; N, 11.8; Cl, 4.35%. Calcd for $C_{45}H_{51}N_7O_3FeCl$: C, 65.2; H, 6.16; N, 11.8; Cl, 4.29%.

By hydrolyzing PMImPe, iron(III) chloride of **2** was obtained. Iron(III) chloride of **1** (350 mg) was dissolved in methanol (15 ml). NaOH (2 mol dm^{-3}, 6 ml) was added to this solution, and the mixture was stirred for 12 h at room temperature. Water (10 ml) was added to this solution, and the methanol was removed by evaporation. The solution was acidified to pH 4.0 by adding dilute hydrochloric acid, and extracted with chloroform. The chloroform layer was dried (Na_2SO_4), and then the solvent was removed by evaporation. Iron(III) chloride of **2**: brown powder; yield, 280 mg (80%). IR: $\nu_{C=O}$ 1500, 1620 (amide), 1720 (carboxylic acid) cm^{-1}. Found: C, 64.7; H, 5.92; N, 12.1; Cl, 4.50%. Calcd for $C_{43}H_{47}N_7O_3FeCl$: C, 64.5; H, 5.87; N, 12.2; Cl, 4.44%.

Synthesis of Iron(III)protoporphyrin IX Bis[N-[*5-(2-methyl-1-imidazolyl)pentyl*]*amide*] *Chloride (Iron(III) Chloride of 3).* Protoporphyrin IX (1.12 g, 2 mmol) and bis(*p*-nitrophenyl) sulfite (4.0 g, 12.3 mmol) were dissolved in 50 ml of DMF–pyridine (1 : 1), after which the solution was allowed to react for 18 h at room temperature. After filtration, the solution was concentrated. The residue was dissolved in dichloromethane, and the insoluble part was removed by filtration; then the solution was poured into diethyl ether–petroleum ether (1 : 1). The crude product was chromatographed on a silica-gel column (3 cm × 20 cm for operating 1 g). The bis(*p*-nitrophenyl ester) was obtained in a 73% yield as the first fraction with dichloromethane–acetone (60 : 1).

The bis(*p*-nitrophenyl ester) (150 mg, 0.18 mmol) and APMIm (4.0 g, 12.3 mmol) were dissolved in a mixture of DMF–dichloromethane (1 : 1) (8 ml), after which the solution was allowed to react for 12 h at room temperature. The resulting solution was concentrated and washed with diethyl ether to remove the *p*-nitrophenol. The crude product was chromatographed on a silica-gel column (1.5 cm × 12 cm). The third fraction chloroform–methanol (4 : 1) was collected and brought to dryness. Protoporphyrin IX bis[*N*-[5-(2-methyl-1-imidazolyl)pentyl]amide] ($P(MImPe)_2$): Found: C, 72.7; H, 7.43; N, 16.3%. Calcd for $C_{52}H_{64}N_{10}O_2$: C, 72.6; H, 7.44; N, 16.3%. IR: $\nu_{C=O}$ 1650, 1555 (amide) cm^{-1}.

The corresponding iron(III) complex of $P(MImPe)_2$ (iron(III) chloride of **3**) was obtained by the above mentioned procedure in a 52% yield. Found: C, 65.7; H, 6.59; N, 14.7; Cl, 3.77%. Calcd for $C_{52}H_{62}N_{10}O_2FeCl$: C, 65.7; H, 6.53; N, 14.7; Cl, 3.74%.

Synthesis of Iron(III)protoporphyrin IX N-[*5-(2-Methyl-1-imidazolyl)pentyl*]*amide* N′-[*ω-Hydroxypoly(ethyleneoxy) carbonylmethyl*]*amide (Iron(III) Chloride of 4).* Iron(III) chloride of **2** was combined with $H_2NCH_2CO(OCH_2CH_2)_nOH$ (Gly-PEG) by the following procedure. Iron(III) chloride of **2** (120 mg, 0.15 mmol) and 1-hydroxybenzotriazole (30 mg, 0.22 mmol) were dissolved in DMF (4 ml). Dicyclohexylcarbodiimide (33 mg, 0.16 mmol) was added to this solution at 0 °C, after which the mixture was allowed to react for 30 min. Gly-PEG (0.5 g, 0.05 mmol of the functional group) and *N*-methylmorpholine (5.5 mg) were then dissolved in DMF (3 ml) and added to this solution. The mixture was stirred for 2 d at room temperature. After concentration, the residue was dissolved in chloroform, and the insoluble part was removed by filtration; then the solution was poured into diethyl ether–ethyl acetate (2 : 1). The crude product was chromatographed on a Sephadex LH-60 column (3 cm × 40 cm for operating 0.2 g). The first fraction with methanol was collected and brought to dryness. The product was reprecipitated from a chloroform–diethyl ether system twice. The degree of incorporation of the complex unit into the functional group of the polymer was determined to be 71% from the absorbance at 385 nm of a chloroform solution of iron(III) chloride of **4** referred to that of the iron(III) chloride of **1**.

Iron(III) chlorides of **5**, **6**, and **7** were synthesized according to Traylor's method.

Other Chemicals. The 2-methylimidazole was purified by recrystallization twice from benzene. The DMF for spectroscopic measurement was treated with molecular sieves (4 Å), and distilled under reduced pressure before use. The ethylene glycol added as antifreeze for spectroscopic measurement was distilled under reduced pressure before use.

Fe(II) Complex Solution. The Fe(III) complex was dissolved in a solvent (DMF/H_2O or pH 10 buffer/ethylene glycol). In the case of PMI-heme and 2-methylimidazole-heme, the ligand was added in this step. Nitrogen gas was bubbled through this solution, and an aqueous solution of sodium dithionite ($[Na_2S_2O_4]/[Fe(III)]=5$) was added to obtain the Fe(II) complex solution.

Measurements. The electronic absorption spectrum was measured with a Union Giken SM-401 spectrophotometer.

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