Synthesis and O_2-binding properties of tetraphenylporphyrinato-iron(II) derivatives bearing a proximal imidazole covalently bound at the β-pyrrolic position

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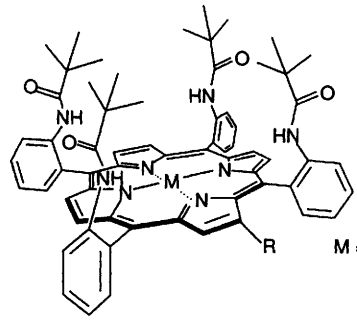
5,10,15,20-Tetrakis(*o*-pivalamidophenyl)porphyrins (TPVP) and their iron(II) derivatives bearing a proximal imidazole covalently bound at the 2-(β-pyrrolic) position have been synthesized. The visible absorption maxima (λ_{max}) of the 2-substituted TPVP with an electron withdrawing group attached is shifted toward the red region (7–11 nm) compared with that of the original TPVP. The iron(II) complexes having an imidazolyl group at the β-pyrrolic position were five coordinated species with an intramolecularly bound base under argon and reversibly formed a stable dioxygen adduct in response to O_2-pressure in toluene at 25 °C. These molecules act as efficient dioxygen carrying molecules. The kinetics of O_2 binding to the 2-substituted Fe(TPVP) complexes are described.

In order to clarify the molecular mechanisms of the active site in hemoproteins, which play various critical roles in biological systems, many synthetic porphyrinatometal complexes have been prepared and their characteristic reactions have been discussed,[1] *e.g.* hemoglobin (hb), myoglobin (mb),[1–9] cytochrome c oxidase,[10] cytochrome P-450,[11,12] and catalase.[13] From the strategic point of view of model synthesis, there are two indispensable targets; (*i*) precise design of a suitable cavity on the porphyrin plane in a geometry (pseudo heme-pocket) in which some substrate can be incorporated or bound and (*ii*) introduction of a proximal base onto the porphyrin structure through a covalent bond. The latter is an especially conclusive factor for the entire functions of the synthetic porphyrin complexes. It is well known that fine tuning of the electron donation from the axial base (imidazole, thiolate, phenolate, *etc.*) to the central metal of the porphyrin complex can substantially improve its electronic structure and reaction capability.

From these standpoints, some attempts to introduce an axial base onto the synthetic porphyrinatometal by a covalent bond have been made;[2b,5a,7,8c] a pioneering compound as model for hb was then 'chelated heme', protoheme IX having a proximal imidazole covalently attached to the propanoic residue.[6a–c] However, a great deal of labour is generally required to attach an axial base to the porphyrin molecule whilst constructing the bulky pocket around the active site on the macrocycle.

If it is possible that the axial base can be introduced onto the highly modified porphyrin derivative already having a pseudo heme-pocket on the ring plane by post-reaction, this methodology would be extremely efficient and would afford great progress in model synthesis of the reaction centre of hemoproteins. In the case of 5,10,15,20-tetraphenylporphyrin (TPP) derivatives, the 2-(β-pyrrolic) position is expected to be a suitable location for functionalization. Thus far, Baldwin and the authors have synthesized a superstructural TPP complex bearing a proximal base at the β-pyrrolic position derived from one of the most prominent hb models, 5,10,15,20-tetraphenylporphyrin capped at the *ortho*-position of each of the phenyl ring by $C_6H_2\{C(O)O[CH_2]_2O\}_4$ (capped heme) and 5,10,15,20-tetrakis(*o*-pivalamidophenyl)porphyrinatoiron [picket-fence heme; Fe(TPVP)] in an independent study.[14,15] However, the functionalization of the β-pyrrolic position of the highly modified TPP derivatives by a post-reaction was not easy to achieve and the yields were rather low. In addition, it has been generally clarified that the redox potentials of the central metal of the 2-substituted TPP change widely depending on the electronic properties of the introduced group; however, their dioxygen binding properties have not been studied in relation to the peripheral substituent.

We have recently found an efficient synthetic procedure for direct functionalization of the β-pyrrolic position of superstructural TPP derivatives. In this paper, we describe in detail the synthesis of Fe(TPVP) derivatives bearing an axial imidazole covalently bound at the β-pyrrolic position through amide or ester linkages as models for the O_2-binding site of hb and mb. These iron(II) complexes formed stable O_2 adducts in toluene at 25 °C. The influence of the 2-substituent on the electronic



M = 2H **a**
= $Fe^{III}Br$ **b'**
= Fe^{II} **b**
= Cu^{II} **c**

R = $-\overset{\overset{O}{\|}}{\underset{H}{N}}C[CH_2]_7N$ (=N) **1**
= $-\overset{\overset{O}{\|}}{\underset{H}{N}}CMe$ **2**
= $-CH_2O\overset{\overset{O}{\|}}{C}[CH_2]_7N$ (=N) **3**
= $-CH_2O\overset{\overset{O}{\|}}{C}[CH_2]_7N$ (=N, Me) **4**
= $-CH_2O\overset{\overset{O}{\|}}{C}Me$ **5**

= −H **6**
= $-NO_2$ **7**
= $-NH_2$ **8**
= −CHO **9**
= $-CH_2OH$ **10**

structure of the porphyrin ring and its O_2-binding properties is described.

Experimental

General

IR spectra were recorded with a JASCO FT/IR-5300 spectrometer. ^1H NMR spectra were recorded on a JEOL GSX-400 instrument. Chemical shifts are expressed in ppm downfield from Me_4Si as an internal standard. Fast atom bombardment (FAB) mass spectra were measured with a JEOL DX-303 spectrometer. Absorption spectra were recorded with a Shimadzu UV-2200 spectrophotometer. Elemental analyses were performed on a Yanagimoto MT3 CHN corder. Thin-layer chromatography (TLC) was carried out on 0.2 mm precoated plates of silica gel 60 F-254 (Merck). Purification was performed by silica gel 60 (Merck) flash-column chromatography.

Materials and solvents

Iodine, silver nitrite, palladium-black, $NaBH_4$, and phosphorous oxychloride were all purchased as special grade from Kanto Chem. Co. and used without further purification. 4-(*N*,*N*-Dimethylamino)pyridine (DMAP) and dicyclohexylcarbodiimide (DCC) were purchased from Tokyo Kasei Co. and used without further purification. Tetrahydrofuran (THF), toluene, benzene and triethylamine (TEA) were purified immediately before use by distillation from sodium. Acetonitrile (MeCN) was purified before use by distillation from diphosphorus pentoxide. Dichloromethane (CH_2Cl_2) was purified before use by distillation from calcium hydride under nitrogen. *N*,*N*-Dimethylformamide (DMF) and 1,2-dimethylimidazole (DMIM) were distilled under argon at reduced pressure. 2-Methylimidazole was purified by recrystallization from benzene several times.

2-Nitro-5,10,15,20-tetrakis(*o*-pivalamidophenyl)porphyrinatocopper(II) [Cu(TPVP-NO$_2$); 7c]. 5,10,15,20-Tetrakis(*o*-pivalamidophenyl)porphyrinatocopper(II) (**6c**) was prepared according to a previous paper.[15] A dry CH_2Cl_2 solution (10 cm^3) of I_2 (0.23 g, 0.9 mmol) and a dry MeCN solution (20 cm^3) of silver nitrite (0.28 g, 1.8 mmol) was added dropwise to a CH_2Cl_2–MeCN (1:1 v/v) (25 cm^3) solution containing **6c** (0.64 g, 0.6 mmol) under argon. Then the mixture was further stirred for 3 h at room temperature under argon. After filtration of the white precipitate, the filtrate was evaporated and the residue was chromatographed on a silica gel flash column using $CHCl_3$–ethyl acetate (15:1 v/v) as the eluent. The major band was collected and evaporated. The residue was then dried at room temperature for several hours *in vacuo* to give a purple crystalline product (**7c**) (0.45 g, 67%), R_f 0.33 [$CHCl_3$–ethyl acetate (4:1 v/v)]; *m*/*z*(FAB) 1118 (M^+) (Found: C, 68.75; H, 5.45; N, 11.05. $C_{64}H_{63}CuN_9O_6$ requires C, 68.75; H, 5.7; N, 11.3%); ν(NaCl)/cm^{-1} 3437 (NH) and 1692 [CO(amide)]; λ_{max}($CHCl_3$)/nm 585, 544 and 585.

2-Nitro-5,10,15-20-tetrakis(*o*-pivalamidophenyl)porphyrin (TPVP-NO$_2$; 7a). To a CH_2Cl_2 solution (20 cm^3) of **7c** (0.5 g, 0.45 mmol), conc. H_2SO_4 (20 cm^3) was added and vigorously stirred for 10 min. The resulting green solution was added dropwise to CH_2Cl_2–ice-water (1:3 v/v) (800 cm^3) and neutralized by $NaHCO_3$ slowly. The mixture was extracted by $CHCl_3$ and washed with water. After drying (Na_2SO_4), the organic layer was evaporated to dryness and the residue was chromatographed on a silica gel flash column using $CHCl_3$–ethyl acetate (4:1 v/v) as the eluent. The major band was collected and the eluent was evaporated. The residue was then dried at room temperature for several hours *in vacuo*, to afford a purple crystalline product (**7a**) (0.45 g, 95%); R_f 0.35 [$CHCl_3$–ethyl acetate 4:1 (v/v)]; *m*/*z*(FAB) 1056 (M^+) (Found: C, 70.55; H, 6.25; N, 11.65. $C_{64}H_{65}N_9O_6$·2H_2O requires C, 70.35; H, 6.2; N, 11.55%); ν(NaCl)/cm^{-1} 3437 (NH) and 1693 [CO(amide)]; δ_H(400 MHz; $CDCl_3$) −2.6 (2 H, s, inner H), 0.2–0.5 (36 H, m, Bu^t), 7.1–8.0 (16 H, m, phenyl H, amide H) and 8.4–9.1 (11 H, m, pyrrole β-H, phenyl H); λ_{max}($CHCl_3$)/nm 653, 595, 553, 522 and 425.

2-Amino-5,10,15-20-tetrakis(*o*-pivalamidophenyl)porphyrin (TPVP-NH$_2$; 8a). 10% Palladium-black (0.16 g) was added to a solution of **7a** (0.2 g, 0.19 mmol) dissolved in CH_2Cl_2–MeOH (1:1 v/v) (20 cm^3) under argon at room temperature. After stirring for a few minutes, $NaBH_4$ (0.23 g, 5.7 mmol) was gradually added to the mixture and the resulting solution was stirred for 30 min at room temperature under argon. After filtration of palladium-black, the filtrate was reduced to a small volume on a rotary evaporator. The residue was then dried at room temperature for several hours under reduced pressure to give a purple crystalline product (**8a**) (0.18 g, 94%); *m*/*z*(FAB) 1026 (M^+) (Found: C, 71.95; H, 6.7; N, 11.25. $C_{64}H_{67}N_9O_4$·3H_2O requires C, 71.15; H, 6.8; N, 11.65%); ν(NaCl)/cm^{-1} 3341, 3428 (NH) and 1684 [CO(amide)]; δ_H(400 MHz; $CDCl_3$) −2.5 (2 H, s, inner H), 0.0–0.4 (36 H, m, Bu^t), 7.1–7.9 (16 H, m, phenyl H, amide H) and 8.6–8.9 (11 H, m, pyrrole β-H, phenyl H); λ_{max}($CHCl_3$)/nm 652, 597, 562, 523 and 411.

2-(8-Imidazol-1-yloctanamido)-5,10,15-20-tetrakis(*o*-pivalamidophenyl)porphyrin [Fe(TPVP-aIm); 1a]. 8-Imidazo-1-yl-octanoic acid hydrochloride was prepared according to a previous procedure described elsewhere.[8c] 8-Imidazol-1-yloctanoic acid hydrochloride (0.12 g, 0.49 mmol) and TEA (0.14 cm^3, 0.98 mmol) were dissolved in dry DMF (5 cm^3) and stirred for 10 min. After removing excess TEA under reduced pressure, **8a** (0.1 g, 98 μmol), DMAP (6.0 mg, 49 μmol) and DCC (0.1 g, 0.49 mmol) were added to the solution and stirred for 48 h at 25 °C in darkness. The deposited dicyclohexylurea (DCU) was filtered off and the filtrate was evaporated to dryness. After the residue had been dissolved in benzene, insoluble DCU was removed again by filtration. The filtrate was concentrated and the residue was chromatographed on a silica gel flash column using $CHCl_3$–MeOH (30:1 v/v) as the eluent. The elution was collected and evaporated to dryness. The residue was then dried at room temperature for several hours *in vacuo*, yielding a purple crystalline product (**1a**) (53.7 mg, 45%); R_f 0.34 [$CHCl_3$–MeOH 15:1 (v/v)]; *m*/*z*(FAB) 1219 (M^+ − H) (Found: C, 73.95; H, 7.2; N, 12.4. $C_{75}H_{84}N_{11}O_5$ requires C, 73.85; H, 6.95; N, 12.65%); ν(NaCl)/cm^{-1} 3429 (NH) and 1690 [CO(amide)]; δ_H(400 MHz; $CDCl_3$) −2.7 (2 H, s, inner H), 0.1–0.3 (36 H, m, Bu^t), 1.2 (10 H, m, –[CH_2]$_5$–), 2.0 [2 H, t, –NHC(=O)CH_2–], 4.0 (2 H, t, –CH_2Im), 6.9–7.9 (19 H, m, amide H, imidazole, phenyl H) and 8.6–8.8 (11 H, m, phenyl H, pyrrole β-H); λ_{max}($CHCl_3$)/nm 646, 590, 550, 518 and 422.

Iron(III) bromide complex (1b'). A dry THF (50 cm^3) solution of **1a** (49.4 mg, 41 μmol) was added dropwise to anhydrous iron(II) bromide (0.86 g, 4 mmol) under dry argon and the mixture was refluxed under argon. The reaction was finished after 4 h. The mixture was then brought to dryness on a rotary evaporator and extracted with $CHCl_3$ and the resulting solution was chromatographed on a silica gel column using $CHCl_3$–MeOH (4:1 v/v) as the eluent. The product was treated with conc. HBr (1 drop) and dried at room temperature for several hours *in vacuo*, to give a dark purple crystalline product (**1b'**) (45.2 mg, 84%), R_f 0.22 [$CHCl_3$–MeOH (15:1 v/v)]; *m*/*z*(FAB) 1352 (M^+ − H) (Found: N, 11.5. $C_{75}H_{82}BrFeN_{11}O_5$ requires N, 11.4%); ν(KBr)/cm^{-1} 3429 (NH) and 1690 [CO(amide)]; λ_{max}($CHCl_3$)/nm 680, 651, 592, 512 and 420.

2-Acetamido-5,10,15-20-tetrakis(*o*-pivalamidophenyl)porphyrin [Fe(TPVP-aAc); 2a]. A dry THF solution (20 cm^3) of **8a** (50 mg, 49 μmol) and TEA (0.68 cm^3, 4.9 mmol) was added to a THF solution (10 cm^3) of acetyl chloride (0.17 cm^3, 2.4 mmol) and further stirred for 5 h at room temperature. The mixture

was extracted with $CHCl_3$ and the organic layer was washed with water and aq. $NaHCO_3$. After drying (Na_2SO_4), the organic layer was evaporated to dryness and the residue was chromatographed on a silica gel flash column using $CHCl_3$–ethyl acetate (10:1 v/v) as the eluent. The major band was collected and reduced to a small volume on a rotary evaporator. The residue was then dried at room temperature for several hours *in vacuo* to give a purple crystalline product (**2a**) (33.2 g, 64%); R_f 0.12 [$CHCl_3$–ethyl acetate (4:1 v/v)]; *m/z*(FAB) 1069 (M^+) (Found: C, 73.8; H, 6.95; N, 11.7. $C_{66}H_{70}N_9O_5$ requires C, 74.15; H, 6.6; N, 11.8%); ν(NaCl)/cm^{-1} 3430 (NH) and 1694 [CO(amide)]; δ_H(400 MHz; $CDCl_3$) −2.7 (2 H, s, inner H), 0.1–0.3 (36 H, m, Bu^t), 2.0 [3 H, s, –C(=O)Me], 7.0–8.1 (16 H, m, amide H, phenyl H) and 8.6–8.8 (11 H, m, pyrrole β-H, phenyl H); λ_{max}($CHCl_3$)/nm 647, 592, 550, 519 and 424.

Iron(III) bromide complex (2b'). The synthetic procedure for the preparation of complex **8b'** was similar to that used for **1b'**, R_f 0.22 [$CHCl_3$–MeOH (15:1 v/v)]; *m/z*(FAB) 1122 (M^+ − Br + H) (Found: N, 11.5 $C_{66}H_{68}BrFeN_9O_5$ requires N, 11.2%); ν(KBr)/cm^{-1} 3430 (NH) and 1686 [CO(amide)]; λ_{max}($CHCl_3$)/nm 680, 652, 590, 512 and 420.

2-Formyl-5,10,15-20-tetrakis(*o*-pivalamidophenyl)porphyrinatocopper(II) [Cu(TPVP–CHO; 9c]. Phosphorus oxychloride (3.5 cm^3, 37.3 mmol) was dropped into DMF (3.5 cm^3) in an ice–water bath and the mixture was stirred for 1 h at room temperature, giving a Vilsmeier reagent. To this solution **6c** (0.2 g, 0.19 mmol) dissolved in dry CH_2Cl_2 (40 cm^3) was added dropwise at 25 °C and refluxed for 15 h, yielding a green solution. Saturated aq sodium acetate (50 cm^3) was added to the mixture at 25 °C and further stirred for 3 h at 40 °C; the colour turned to red–purple. The mixture was extracted by $CHCl_3$ and washed with water. After drying (Na_2SO_4), the organic layer was evaporated to dryness and the residue was chromatographed on a silica gel flash column using $CHCl_3$–ethyl acetate (6:1 v/v) as the eluent. The major band was collected and the eluent was evaporated. The residue was dried at room temperature for several hours *in vacuo* to give a purple crystalline product (**9c**) (0.16 g, 78%), R_f 0.33 [$CHCl_3$–ethyl acetate (4:1 v/v)]; *m/z*(FAB) 1100 (M^+ − H) (Found: C, 71.1; H, 6.3; N, 10.45. $C_{65}H_{64}CuN_8O_5$ requires C, 70.9; H, 6.05; N, 10.15%); ν(NaCl)/cm^{-1} 1690 [CO(amide)] and 1674 [CO(formyl)]; λ_{max}($CHCl_3$) 587, 545 and 424 nm.

2-Formyl-5,10,15-20-tetrakis(*o*-pivalamidophenyl)porphyrin (TPVP-CHO; 9a). Demetallation of **9c** was performed in a similar manner as described above in the synthesis of **7a** to give **9a** (0.12 g, 85%); R_f 0.33 [$CHCl_3$–ethyl acetate (4:1 v/v)]; *m/z*(FAB) 1039 (M^+) (Found: C, 75.5; H, 6.75; N, 11.05. $C_{65}H_{66}N_8O_5$ requires C, 75.1; H, 6.4; N, 10.8%); ν(NaCl)/cm^{-1} 1690 [CO(amide)] and 1674 [CO(formyl)]; λ_{max}($CHCl_3$)/nm 655, 596, 556, 522 and 428.

2-Hydroxymethyl-5,10,15-20-tetrakis(*o*-pivalamidophenyl)-porphyrin (TPVP-mOH; 10a). $NaBH_4$ (41.5 mg, 1.1 mmol) was added to a solution of CH_2Cl_2–MeOH (1:3 v/v) (8 cm^3) containing **9a** (0.11 g, 0.11 mmol) under argon at room temperature and stirred for 15 min. After adding water to the solution, the mixture was extracted with $CHCl_3$ and the organic layer was washed with water and aq. $NaHCO_3$. After drying (Na_2SO_4), the organic layer was evaporated to dryness and the residue was chromatographed on a silica gel flash column using $CHCl_3$–MeOH (10:1 v/v) as the eluent. The major band was collected and reduced to a small volume on a rotary evaporator. The residue was then dried at room temperature for several hours *in vacuo* to give a purple crystalline product (**10a**) (0.11 g, 94%); R_f 0.18 [$CHCl_3$–ethyl acetate (4:1 v/v)]; *m/z*(FAB) 1040, (M^+ − H) (Found: C, 74.95; H, 6.3; N, 10.8. $C_{65}H_{68}N_8O_5$ requires: C, 74.95; H, 6.6; N, 10.75%); ν(NaCl)/cm^{-1} 1692 [CO(amide)]; λ_{max}($CHCl_3$)/nm 640, 585, 542, 511 and 417.

2-(8-Imidazol-1-yloctanoyloxymethyl)-5,10,15-20-tetrakis(*o*-pivalamidophenyl)porphyrin [Fe(TPVP-mIm); 3a]. 8-Imidazol-1-yloctanoic acid hydrochloride (90.1 mg, 0.37 mmol) and TEA (0.1 cm^3, 0.74 mmol) were dissolved in dry DMF (4 cm^3) and stirred for 10 min. After removing TEA under reduced pressure, **10a** (76 mg, 73 μmol), DMAP (4.5 mg, 37 μmol) and DCC (75.4 mg, 0.37 mmol) were added to the solution and stirred for 84 h at room temperature in darkness. The deposited DCU was filtered off and the filtrate was evaporated to dryness. After the residue had been dissolved in benzene, insoluble DCU was removed again by filtration. The filtrate was concentrated and the residue was chromatographed on a silica gel flash column using $CHCl_3$–MeOH (30:1 v/v) as the eluent. The eluted solution was collected and evaporated to dryness. The residue was then dried at room temperature for several hours *in vacuo* to afford a purple crystalline product (**3a**) (80 mg, 89%); R_f 0.36 [$CHCl_3$–MeOH (15:1 v/v)]; *m/z*(FAB) 1233, (M^+ − H) (Found: C, 73.7; H, 6.5; N, 11.05. $C_{76}H_{84}N_{10}O_6$ requires C, 74.0; H, 6.85; N, 11.35%); ν(NaCl)/cm^{-1} 1738 [CO(ester)] and 1690 [CO(amide)]; δ_H(400 MHz; $CDCl_3$) −2.6 (2 H, s, inner H), 0.0–0.1 (36 H, m, Bu^t), 1.2 (10 H, m, –[CH_2]$_5$–), 2.3 [2 H, t, –OC(=O)CH_2–], 4.0 (2 H, t, –CH_2Im), 5.3 [2 H, s, Por-CH_2OC(=O)], 6.9, 7.0, 7.3 (3 H, 3 s, imidazole), 7.2 (4 H, m, amide H), 7.5 (4 H, m, phenyl H), 7.8–7.9 (8 H, m, phenyl H) and 8.7–8.8 (11 H, m, phenyl H, pyrrole β-H); λ_{max}($CHCl_3$)/nm 641, 586, 543, 511 and 417.

Iron(III) bromide complex (3b'). The synthetic procedure for formation of complex **3b'** was similar to that used for **1b'**, R_f 0.35 [$CHCl_3$–MeOH (15:1 v/v)]; *m/z*(FAB) 1288, (M^+ − Br + H) (Found: N, 10.15. $C_{76}H_{82}BrFeN_{10}O_6$ requires N, 10.25%); ν(KBr)/cm^{-1} 1738 [CO(ester)] and 1690 [CO(amide)]; λ_{max}($CHCl_3$)/nm 680, 651, 584, 509 and 415.

8-(2-Methylimidazol-1-yl)octanoic acid hydrochloride. Diphenylmethyl 8-bromooctanoate was synthesized according to Collman's procedure.[2b] LiH (0.13 g, 16.2 mmol) was added to a THF solution (100 cm^3) of 2-methylimidazole (1.48 g, 18.0 mmol) under argon and the mixture, which was refluxed for 24 h, changed to a pale yellow homogeneous solution. Then a THF solution (50 cm^3) of the above octanoate (7.0 g, 18.0 mmol) was added to this solution and refluxed for a further 12 h. The solvent was then removed by evaporation and $CHCl_3$ was added to the residue. The solution was washed with water and dried (Na_2SO_4). The solvent was removed on a rotary evaporator and the remaining yellow oil purified by a silica gel column chromatography using $CHCl_3$–MeOH (20:1 v/v) as the eluent to give a pale yellow oil (4.0 g, 58%); R_f 0.23 [$CHCl_3$–MeOH (20:1 v/v)]; ν(NaCl)/cm^{-1} 1736 [CO(ester)].

The oil (3.4 g, 8.6 mmol) was dissolved in glacial acetic acid (50 cm^3). Dry HCl was passed through the solution with vigorous stirring for 1 h and further stirred for 1.5 h at room temperature. Acetic acid and HCl were removed under reduced pressure. The residue was dissolved in water and washed with diethyl ether to produce a pale yellow–white solid. Drying *in vacuo* afforded a white solid (1.6 g, 82%); ν(NaCl)/cm^{-1} 1734 [CO(ester)]; δ_H(400 MHz; CD_3OD) 1.3–1.8 (10 H, m, –CH_2–), 2.2 (2 H, t, –CH_2CO_2H), 2.6 (3 H, s, 2-MeIm), 4.0 (2 H, t, NCH_2–), 7.4 and 7.5 (2 H, 2 s, imidazole).

2-[8-(Methylimidazol-1-yl)octanoyloxymethyl]-5,10,15-20-tetrakis(*o*-pivalamidophenyl)porphyrin [TPVP-mmIm; 4a). The procedure for the synthesis of **4a** was similar to that used for **3a**, except for using 8-(2-methylimidazol-1-yl)octanoic acid hydrochloride. Finally a purple crystalline product (**4a**) (50 mg, 65%) was obtained. R_f 0.46 [$CHCl_3$–MeOH (10:1 v/v)]; *m/z*-(FAB) 1248 (M^+) (Found: C, 74.5; H, 7.1; N, 11.5. $C_{77}H_{86}N_{10}$-O_6 requires C, 74.15; H, 6.95; N, 11.25%); ν(NaCl)/cm^{-1} 1738 [CO(ester)] and 1690 [CO(amide)]; δ_H(400 MHz; $CDCl_3$) −2.6 (2 H, s, inner H), 0.0–0.1 (36 H, m, Bu^t), 1.3 (10 H, m, –[CH_2]$_5$–), 2.3 [2 H, t, –OC(=O)CH_2–], 2.4 (3 H, s, 2-MeIm), 3.8 (2 H, t, –CH_2Im), 5.3 [2 H, s, Por-CH_2OC(=O)], 6.8, 6.9

(2 H, 2 s, imidazole), 7.2 (4 H, m, amide), 7.5–7.9 (12 H, m, phenyl H) and 8.7–8.8 (11 H, m, phenyl H, pyrrole β-H); $\lambda_{max}(CHCl_3)$/nm 641, 586, 543, 511 and 417.

Iron(III) bromide complex (4b'). The synthetic procedure for the preparation of complex **4b'** was similar to that used for **1b'**, R_f 0.33 [$CHCl_3$–MeOH (10:1 v/v)]; *m/z* 1301 (M^+ – Br) (Found: N, 10.0. $C_{77}H_{84}BrFeN_{10}O_6$ requires 10.15%); ν(KBr)/cm^{-1} 1732 [CO(ester)] and 1692 [CO(amide)]; $\lambda_{max}(CHCl_3)$/nm 680, 651, 584, 509 and 415.

2-Acetoxymethyl-5,10,15-20-tetrakis(*o*-pivalamidophenyl)-porphyrin (TPVP-mAc; 5a). A dry THF solution (15 cm^3) of **10a** (62.4 mg, 60 μmol) and TEA (0.42 cm^3, 3.0 mmol) was added to THF solution (5 cm^3) of acetyl chloride (0.21 cm^3, 3.0 mmol) and further stirred for 1 h at room temperature. The mixture was extracted with $CHCl_3$ and the organic layer was washed with water and aq $NaHCO_3$. After drying (Na_2SO_4), the organic layer was evaporated to dryness and the residue was chromatographed on a silica gel flash column using $CHCl_3$–ethyl acetate (10:1 v/v) as the eluent. The major band was collected and reduced to a small volume on a rotary evaporator. The residue was then dried at room temperature for several hours *in vacuo* to give a purple crystalline product (**5a**) (50.6 g, 79%); R_f 0.32 [$CHCl_3$–ethyl acetate (5:1 v/v)]; *m/z*(FAB) 1083 (M^+) (Found: C, 74.6; H, 6.2; N, 10.5. $C_{67}H_{70}N_8O_6$ requires C, 74.3; H, 6.5; N, 10.35%); ν(NaCl)/cm^{-1} 1742 [CO(ester)] and 1692 [CO(amide)]; δ_H(400 MHz; $CDCl_3$) −2.6 (2 H, s, inner H), 0.0–0.1 (36 H, m, Bu^t), 2.1 [3 H, s, –C(=O)Me], 5.3 [2 H, s, Por-CH_2OC(=O)], 7.1–7.2 (4 H, m, amide H), 7.5–7.9 (12 H, m, phenyl H), 8.7 (4 H, m, phenyl H) and 8.8 (7 H, m, pyrrole β-H); $\lambda_{max}(CHCl_3)$/nm 643, 587, 545, 512 and 419.

Iron(III) bromide complex (5b'). The procedure for the synthesis of complex **5b'** was similar to that used for **1b'**, R_f 0.32 [$CHCl_3$–MeOH (15:1 v/v)]; *m/z*(FAB) 1137 (M^+ – Br) (Found: N, 9.1. $C_{67}H_{68}BrFeN_8O_6$ requires N, 9.2%); ν(KBr)/cm^{-1} 1746 [CO(ester)] and 1692 [CO(amide)]; $\lambda_{max}(CHCl_3)$/nm 670, 645, 575, 505 and 415.

Iron(II) complex. Reduction to the porphyrinatoiron(II) complex was carried out by using toluene–aq. $Na_2S_2O_4$ in a heterogeneous two-phase system under anaerobic conditions as previously reported.[8b–d] After separation of the two phases, the organic layer containing the reduced compound was dried (Na_2SO_4) and transferred into the cuvette under argon atmosphere.

Equilibrium measurements

O_2-Binding to the porphyrinatoiron(II) complex was expressed by reaction (1) (Por = porphyrinate, B = axial base). In the

$$Fe(Por)B + O_2 \overset{K(O_2)}{\rightleftharpoons} Fe(Por)B(O_2) \quad (1)$$

case of porphyrinatoiron(II), without the proximal imidazole intramolecularly attached to the structure, an excess of 1,2-dimethylimidazole (DMIM) (0.1–0.2 mol dm^{-3}) was added to the toluene solution. The O_2-binding affinity {O_2 pressure at half O_2-binding for the porphyrinatoiron(II), $P_{\frac{1}{2}}(O_2) = 1/[K(O_2)]$} was determined as described previously.[8b,c,16,17] For visible absorption spectroscopy, heme concentrations of 2×10^{-5} mol dm^{-3} were used. The spectra were recorded within the range of 700–360 nm.

Kinetic measurements

Kinetic studies were performed by using a Unisoku TSP-600 time-resolved spectrophotometer system. Laser flash photolysis was carried out by using a Continuam Surelite I-10 Q-switched Nd:YAG laser. This generated a second-harmonic (532 nm) pulse of 6 ns duration with an energy of 200 mJ per pulse; a repetition rate of 10 Hz was used for the excitation of sample solution. The output signal from a photomultiplier was recorded on a Hewlett Packard digitizing oscilloscope 54510B. For steady-state irradiation, a 150 W Xenon lump was used as the monitor light source. Heme concentrations of 1×10^{-5} mol dm^{-3} were used and most experiments were carried out at 25 ± 0.2 °C.

O_2-Binding kinetics were measured by a competitive re-binding technique using Gibson's equation.[16–18] Photolysis of Fe(Por)B(CO) in the presence of CO and O_2 yields the five-coordinated Fe(Por)B complex which subsequently adds dioxygen in a fast step owing to the large value of $k_{on}(O_2)$. Then the subsequent return of Fe(Por)B(O_2) to Fe(Por)B(CO) in a slow step gives the O_2-binding constants [eqn. (2)].

$$Fe(Por)B(CO) \underset{k_{on}(CO)}{\overset{k_{off}(CO)}{\rightleftharpoons}} Fe(Por)B \underset{k_{off}(O)_2}{\overset{k_{on}(O_2)}{\rightleftharpoons}} Fe(Por)B(O_2) \quad (2)$$

Porphyrinatoiron derivatives have much higher $k_{on}(O_2)$ and $k_{off}(O_2)$ values than those of CO, allowing direct determination of $k_{on}(O_2)$ from a plot of eqn. (3).

$$k_{obs}(fast) = k_{on}(O_2)[O_2] + k_{off}(O_2) \quad [k_{on}(O_2)/k_{off}(O_2) = K(O_2)] \quad (3)$$

The rate constant for the slower process is given by eqn. (4).

$$\frac{1}{k_{obs}(slow)} = \frac{K(O_2)[O_2]}{k_{on}(CO)[CO]} + \frac{1}{k_{on}(CO)[CO]} + \frac{1}{k_{off}(O_2)} \quad (4)$$

Therefore, the slope of the plots of $k_{on}(CO)/k_{obs}(slow)$ *vs.* $[O_2]$ at fixed [CO] gives $K(O_2)$ accurately using eqn. (5).[17] The

$$\frac{k_{on}(CO)[CO]}{k_{obs}(slow)} = K(O_2)[O_2] + \frac{k_{on}(CO)[CO]}{K_{off}(O_2)} + 1 \quad (5)$$

required $k_{on}(CO)$ is simply obtained from photolysis in the absence of O_2.

Results and discussion

Synthesis and structure

A mild and efficient procedure for direct functionalization of the β-pyrrolic position of the superstructural tetraphenylporphyrin derivatives has been established. For designing new analogues of hemoglobin, a simple method for the introduction of an alkylimidazolyl group to the porphyrin by a post-reaction would be extremely useful. We presented in detail the synthetic procedure for the preparation of TPVP derivatives bearing proximal imidazoles at the β-pyrrolic position. The functional groups introduced onto the β-pyrrolic position of TPVP were selected to be amino and hydroxymethyl groups, which are easily converted to the amide and ester bonds. All the intermediate porphyrins except for 2-aminoporphyrin (**8a**) were stable in air or light.

Cu(TPVP–NO_2) (**7c**) could be prepared by treatment of Cu(TPVP) (**6c**) with iodine and silver nitrite in CH_2Cl_2–MeCN at room temperature (67%). Crossley *et al.* provided a general method for the efficient synthesis of 2-nitro-TPP and showed that nitration of the porphyrin was dependent on the co-ordinated central metal, in particular the Cu^{II} complex was cleanly and specifically nitrated on the β-pyrrolic position. In contrast capped porphyrinatozinc(II) was readily nitrated by the same methods.[14] Certainly, Zn(TPVP) was nitrated to give Zn(TPVP–NO_2), but in this case, the reaction was slower and some polar ring-opened products were also obtained.

Table 1 Visible absorption spectral data of free base 2-substituted TPVP derivatives in $CHCl_3$ at 25 °C

Derivative	λ_{max}/nm
6a	417, 511, 542, 585, 640
2a	424, 519, 550, 592, 647
5a	419, 512, 545, 587, 643
7a	425, 522, 553, 595, 653
8a	411, 523, 562, 597, 652
9a	428, 522, 556, 596, 655
10a	417, 511, 542, 585, 640

Demetallation of **7c** with conc. H_2SO_4 proceeded smoothly and gave the corresponding TPVP–NO_2 in 95% yield. The TPVP–NO_2 (**7a**) was hydrogenated to TPVP–NH_2 (**8a**) in almost quantitative yields with $NaBH_4$ in MeOH in the presence of a 10% palladium-black. TPVP–NH_2 was unstable in silica gel chromatography. Momenteau *et al.* reported the same phenomenon concerning unstable 2-amino-TPP and concluded that the β-aminoporphyrin behaved as an enamine or imine rather than an aromatic amine.[19] For example, under strongly acidic conditions protonated *meso*-imine tautomers were formed, but otherwise *meso*-aminoporphyrins appeared to behave as aromatic amines, forming diazonium salts. The difference in behaviour of the aminoporphyrins was a consequence of the fact that aromatic 18π electron delocalization of the porphyrin system did not require full conjugation of the β,β-pyrrolic double bonds. However, the β-aminoporphyrin showed amine reactivity. TPVP–NH_2 (**8a**) was quantitatively acylated on the amino nitrogen without β-acylenamine; treatment of **8a** with acetyl chloride and DMAP yielded the β-acetamide TPVP (**2a**) (64%).

The formyl group was introduced onto the β-pyrrolic position of Cu(TPVP) using the Vilsmier formylation.[15] After hydrolysis of the green coloured iminium compound, the Cu(TPVP–CHO) (**9c**) was obtained (78%). Further the demetallation proceeded in the same manner as described for **7a** in a good yield (85%). This was different from Momenteau's results in which demetallation of Cu(TPP) under various sulfonic acid conditions did not yield the corresponding free-base porphyrin. **9a** was reduced by $NaBH_4$ and palladium-black to give stable TPVP–CH_2OH (**10a**). Of course, the hydroxymethyl group of **10a** was easily acylated by acid chloride or acid anhydride with DMAP.

Introduction of an axial base onto the amino or hydroxymethyl group at the β-pyrrolic position of TPVP through an amide or ester bond was achieved using 8-imidazol-1-yloctanoic acid and DCC in DMF at room temperature, leading to the corresponding free base porphyrins (**1a**, **3a**, **4a**). The length of the alkyl unit is determined to be eight, which is adequate for imidazole binding to the central iron(II). All the compounds were characterized physicochemically (see Experimental section).

The positions of the Soret and Q-band maxima (λ_{max}) for the obtained 2-substituted TPVP were measured in $CHCl_3$ (Table 1). It is known that the λ_{max} value of 2-substituted porphyrins are always influenced by the inductive effect of the peripheral substituents. Crossley *et al.* have studied the spectroscopy and electrochemistry of a series of 2-substituted Cu(TPP) complexes.[20] The substituent has a considerable effect on the energies of the two highest occupied molecular orbitals (a_{2u} and a_{1u}) and the effect is felt much more strongly on the a_{1u} orbital, which has significant electron density associated with the β-pyrrolic position of the metalloporphyrins. In the case of the 2-substituted TPVP having an electron-withdrawing group at the β-pyrrolic position (**1a**, **2a**, **7a**, **9a**), the λ_{max} of the Soret bands are shifted toward the red region, 7–11 nm, compared with those

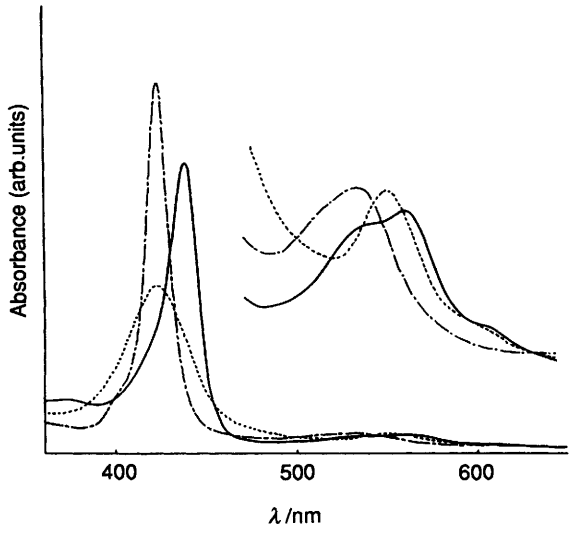


Fig. 1 Visible absorption spectral changes of Fe(TPVP–mmIm) (**4b**) in toluene at 25 °C: (——), deoxy; (– – – –), oxy; (— · — · —), carbonyl

of the original TPVP. Furthermore, the strongly electron withdrawing groups at the β-pyrrolic position often caused a 'Rhodo' type (band IV > III > I > II) spectrum.[19] The visible absorption spectral patterns of **7a** and **9a** also displayed the Rhodo type, which resulted from the strong asymmetric delocalization of the π-electron density due to the nitro and formyl groups.

Iron insertion into the 2-substituted free base TPVP could be accomplished by the usual methods using $FeBr_2$. The reduction of Fe^{III} (TPVP) bearing a proximal imidazole covalently bound at the β-pyrrolic position (**1b'**, **3b'**, **4b'**) with aqueous $Na_2S_2O_4$ in a two-phase system (toluene–water) under anaerobic conditions produced pale red solutions. The spectra of the reduced porphyrinatoiron(II)s in toluene are clearly distinct from both those of four-coordinated and typical bis-*N*-ligated six coordinated Fe(TPP) derivatives (Table 2). Their absorption spectra are characterized by two broad visible bands (near 540 and 560 nm) with one shoulder and a Soret band at 440 nm (Fig. 1) and are quite similar to those obtained with well identified mono-*N*-ligated five coordinated species.[16] These visible spectra did not change in the temperature range of −10 to *ca.* 60 °C. Thus, these spectra are assigned to high-spin, five-coordinated species on the basis of their absorptions. This shows that typical five-coordinated complexes with an intramolecular imidazole bound in the fifth axial coordinating position of iron(II) are obtained regardless of either the linkage form (amide or ester) and the presence of a 2-methyl group in the imidazole ring.

O_2 and CO binding affinity

The addition of O_2 and CO to the toluene solution of the deoxy complex of Fe^{II}(TPVP) bearing a covalently bound axial imidazole (**1b**, **3b**, **4b**) resulted in stable O_2 and CO adducts, respectively, on the basis of their absorption spectra (Table 2). The O_2-adduct spectra changed reversibly in response to O_2 pressures (Fig. 1). The half-lifetimes ($\tau_{\frac{1}{2}}$) of the O_2-adduct with respect to Fe^{III} porphyrins were 27 h for **3b** and **4b**, and 6 h for **1b** in toluene at 25 °C. The difference in $\tau_{\frac{1}{2}}$ between **1b** and **3b** suggested that the stability of the O_2 adduct is dependent on the linkage form at the β-pyrrolic position.

Spectroscopic dioxygen titrations of **4b** were carried out. The isosbestic points were maintained in all titrations. The dioxygen complex changed to the corresponding CO adduct upon bubbling carbon monoxide gas through the solution. The

Table 2 Visible absorption spectral data of porphyrinatoiron(II) derivatives in toluene at 25 °C

Derivative	λ_{max}/nm		
	Deoxy	Oxy	Carbonyl
Fe(TPVP–aIm) **1b**	(608), 565, 540, 440	551, 430	543, 429
Fe(TPVP–mIm) **3b**	(606), 562, 540, 437	546, 423	541, 423
Tailed heme[a]	(608), 558, 536, 438	546, 425	540, 425
Fe(TPVP–mmIm) **4b**	(608), 561, 535, 439	550, 422	534, 422
Fe(TPVP–aAc) **2b**(DMIM)	(609), 565, 539, 440	554, 434	539, 427
Fe(TPVP–mAc) **5b**(DMIM)	(605), 560, 532, 437	548, 421	536, 421
Fe(TPVP)(DMIM)	(608), 562, 535, 439	544, 421	539, 424

[a] From ref. 1*b*.

Table 3 O_2 and CO binding parameters of porphyrinatoiron(II) derivatives in toluene at 25 °C

Derivation	$P_{\frac{1}{2}}(O_2)$/Torr	$k_{on}(O_2)/10^8$ dm^3 mol^{-1} s^{-1}	$k_{off}(O_2)/10^4$ s^{-1}	$k_{on}(CO)/10^6$ dm^3 mol^{-1} s^{-1}
Fe(TPVP–aIm) **1b**	4.6	3.7	1.3	11
Fe(TPVP–mIm) **3b**	0.29	6.4	0.14	31
Tailed heme[a]	0.58	4.3	0.29	36
Fe(TPVP–mmIm) **4b**	38	1.6	4.6	2.9
Fe(TPVP–aAc) **2b** (DMIM)	230	1.5	26	1.1
Fe(TPVP–mAc) **5b** (DMIM)	49	1.7	6.3	1.2
Fe(TPVP) (DMIM)[b]	37	1.2	3.4	1.6
a	38	1.1	4.6	1.4

[a] From ref. 16. [b] From ref. 8*b*.

value for $P_{\frac{1}{2}}(O_2)$ was found to be independent of the wavelength used to determined the extent of dioxygenation (Table 3). On the other hand the $P_{\frac{1}{2}}(O_2)$ values of **1b** and **3b** were determined kinetically (see Experimental section).

The O_2-binding affinities of **3b** and **4b** were almost the same as those of the 5,10,15-tris(*o*-pivalamido)-20-(5-imidazolylvaleramidophenyl)porphyrinatoiron(II) complex (tailed heme) and Fe(TPVP)(DMIM) complex, respectively.[16] However, the O_2-binding affinity of Fe(TPVP–aIM)(**1b**) was six-fold lower than that of the tailed heme. To estimate the electronic effect of the 2-substituted group for dioxygenation, the $P_{\frac{1}{2}}(O_2)$ values of Fe(TPVP) having an acetamide (**2b**) or acetoxymethyl group (**5b**) at the β-pyrrolic position have been determined in the presence of a large excess of DMIM in toluene. The reaction of the heme with the sterically hindered base DMIM affords only a five-coordinated high spin species owing to the repulsive interaction between the hydrogen atoms of the 2-methyl group and the porphyrin ring. Similar to **1b**, the $P_{\frac{1}{2}}(O_2)$ of the acetamide type (**2b**) was also larger than that of the acetoxymethyl derivatives (**5b**).

In general, dioxygenation of the porphyrinatoiron complexes can be altered by the inductive effect in the porphyrin plane. Basolo *et al.* studied ligation and dioxygenation of the 2-nitro capped heme in order to determine the effect of an electron-withdrawing group.[4b] Their results showed that the flow of electron density away from the system retarded dioxygenation. Traylor *et al.* also suggested that side-chain electron donation in the chelated heme increased the O_2-binding affinity.[21]

Therefore, these results show that the electron-withdrawing amide group at the β-pyrrolic position of **1b** and **2b** reduced the electron density of the central iron, inducing reduction of the O_2-binding affinity. The red shifted Soret band absorption maxima of O_2 and CO complexes of **1b**, compared with those of **3b** and the tailed heme, also indicate extension of π-electron delocalization in the porphyrin ring.

A change in the covalently bound axial base from imidazolyl to a 2-methylimidazolyl group produces a decrease in the O_2-binding affinity. This effect is due to the steric hindrance of the 2-methyl group which resists the metal entering the porphyrin plane on deoxygenation.[22] The $P_{\frac{1}{2}}(O_2)$ value of **3b**, 0.29 Torr,† and **4b**, 38 Torr, which is sufficiently high to act as an O_2-binding site of mb and hb models. The thermodynamic parameters for the O_2-binding, enthalpy changes (ΔH) and entropy changes (ΔS) for **4b** were estimated to be -61 kJ mol^{-1} and -178 J K^{-1} mol^{-1}, respectively, comparable to those of the Fe(TPVP)(DMIM) complex and hb.[16]

Kinetics of O_2 and CO binding

In order to elucidate the O_2 and CO binding properties of the porphyrinatoiron(II) bearing a covalently bound proximal imidazole, the dynamics of binding were explored by laser flash photolysis.

When a toluene solution of the Fe(Por)B(CO) ([heme] = 1×10^{-5} mol dm^{-3}) was photolysed, linear decay plots of log ΔA *vs.* t were obtained. This indicates a clean monophasic rebinding and the value of $k_{on}(CO)$ is easily obtained. Kinetic parameters for the O_2 and CO binding to the porphyrinatoiron complexes are also summarized in Table 3.

The lower O_2-binding affinities of the **1b** and **2b** complexes (amide type) compared with **3b** and **5b** (methylene ester type) arise mainly from the increase in the O_2-dissociation rate constants. Several investigations suggested that the following factors control the $k_{off}(O_2)$ of the synthetic hemes[6a,d,16,17] (*i*) proximal base ligation as a fifth ligand of hemes, (*ii*) distal steric hindrance and (*iii*) local polarity around the O_2-binding site (solvent effect, electrostatic interactions, *etc.*). The chelated protoheme was compared with two analogues in which the two vinyl groups are replaced by either two electron-donating ethyl groups or two electron-withdrawing acetyl groups.[21] In this series, the $k_{off}(O_2)$ increased in the order ethyl < vinyl < acetyl with a consequent lowering of the O_2-binding affinity. It is assumed that introduction of the amide groups directly onto the β-pyrrolic position of the TPVP ring causes a decrease in the electron density of the central metal and weakens the dioxygenated species, as a result of the increasing $k_{off}(O_2)$.

† 1 Torr = 133.322 Pa.

In this paper we demonstrated a mild and efficient synthetic methodology for introducing any functional group onto the β-pyrrolic position of a highly modified tetraphenylporphyrinatometal (*i.e.* picket-fence porphyrinate) by post-reaction. These results would be very useful and would afford great progress in a synthetic approach for elucidation of the mechanism of hemoprotein function. The O_2-binding equilibria and kinetics of Fe(TPVP) bearing a proximal imidazole covalently bound at the β-pyrrolic position were discussed. The introduction of the alkyl imidazole through a methylene ester linkage directly onto the porphyrin structure has not affected the electronic property of the porphyrin ring and O_2-binding parameters of the heme. These porphyrin derivatives are expected to act as efficient O_2-carrying molecules in homogeneous or heterogeneous solution systems and even in the solid state. As a red blood cell substitute in aqueous media, we have developed a hybrid system of a phospholid vesicle embedded heme.[8a] In the case of Fe(TPVP) bearing a covalently bound axial imidazole, it is not necessary to add an external imidazole in the bilayer, affording formation of a stable phospholipid vesicle. A study of the O_2-binding ability of Fe(TPVP) having a proximal imidazole under physiological conditions (aqueous medium, pH 7.4, 37 °C) is now in progress.

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