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Double-Sided Porphyrinatoiron(II) Bearing Covalently Bound Imidazole. An Efficient Oxygen-Carrier Molecule Composed by 8 Ester Bonds

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Double-sided porphyrinatoiron(II) bearing covalently bound axial imidazole, 5,10,15-tris(2,6-bis(3,3-dimethylbutyryloxy)phenyl)-20-(2-(3,3-dimethylbutyryloxy)-6-(5-imidazolylvaleroyloxy)phenyl)porphyrinatoiron (**1b**), was synthesized: The substituents of **1b** are bound with the porphyrin only through ester bonds. **1b** formed a stable O_2 adduct reversibly in toluene at 25 °C or with a lipid surfactant under physiological conditions.

As a model compound of hemoglobin (Hb) and myoglobin (Mb), both-faces hindered porphyrinatoiron complexes have been prepared and their O_2 and CO binding behavior was discussed extensively.[1-4] The most unique feature of them is prevention against the irreversible oxidation of the porphyrinatoirons *via* μ-dioxo dimer formation.

Recently we have reported synthesis of highly symmetric tetraphenylporphyrins, "double-sided porphyrins", bearing 8 ester groups on the both sides of the porphyrin plane and O_2 and CO binding property of their iron complexes.[5] Advantages of the double-sided porphyrinatoirons are (1) removal of complexity of diastereoisomeric properties in the preparation and (2) variation in the O_2 binding affinity and/or kinetics by the pocket-size of porphyrin.[5b,c] However there remains a couple of unsolvable problems that an axial base is to be externally added and that the O_2

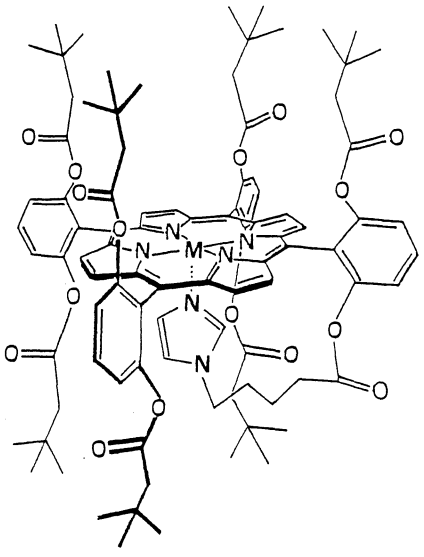

Fig. 1. Double-sided porphyrin bearing covalently bound imidazole.

binding affinity is much lower than that of Hb and Mb. Porphyrin derivatives covalently combined with axial base have been synthesized: chelated,[6] tailed picket-fence,[7] ligand-appended,[8] hanging-base,[1] capped-strapped,[3] and doubly-bridged,[4] porphyrinatoiron. Behaviors of their O_2 binding have been discussed.

This paper reports the synthesis of new double-sided porphyrinatoiron(II) bearing both ester-cavities and covalently bound axial imidazole (Fig. 1) through a convenient route. The high O_2 binding affinity at room temperature and ligand binding property are described.

5,10,15-Tris(2,6-bis(3,3-dimethylbutyryloxy)phenyl)-20-(2-(3,3-dimethylbutyryloxy)-6-hydroxyphenyl) porphyrin was synthesized by condensation of 5,10,15,20-tetrakis(2,6-bis(hydroxy)phenyl) porphyrin with 7.2 times mole of 3,3-dimethylbutyrylchloride in dry terahydrofuran (THF) (10%). This compound was allowed to react with 5-(imidazolyl)valeroyl chloride in the presence of 4-(dimethylamino)pyridine in dry acetonitrile to give **1a** (54%).[9] Iron was inserted by refluxing with $FeBr_2$/THF in the presence of 2,6-lutidine to give **1b′**.[9] All preparative steps including purification were carried out in a dark room. **1b′** was converted to the Fe(II) derivative **1b** by reduction using aqueous $Na_2S_2O_4$ in a heterogeneous two-phase system under N_2 atmosphere.[5a] The visible absorption spectrum of **1b** in toluene solution showed deoxy state (λ_{max}; 555, 535, and 432 nm) assigned to five N-coordinated porphyrinatoiron(II).

The visible absorption spectrum of the deoxy **1b** changed to that of O_2 adduct on exposure to O_2 (λ_{max}(toluene); 544 and 420 nm). The O_2 adduct changed to the corresponding CO adduct on bubbling CO gas through the solution (λ_{max}(toluene); 540 and 421 nm). The half-life of the O_2 adduct with respect to the irreversible oxidation of Fe(II) to Fe(III) in toluene at 25 °C was >2 days. Reversible O_2 binding at room temperature was also successfully observed for **1b** solubilized with a phospholipid ,*e.g.*, dipalmitoylphosphocholine (DPPC) in an aqueous medium.[10] The phospholipid vesicle embedded with **1b** is an efficient dioxygen carrier under physiological condition.

The CO bonding property of **1b** was studied by infrared spectroscopy. Difference spectrum of the deoxy **1b** vs. the CO-**1b** adduct gave ν(CO) at 1962 cm^{-1} ([Fe]=10 mmol dm^{-3} in benzene), which is much lower than that of the 5,10,15,20-tetrakis (2,6-bis(pivaloyloxy)phenyl)porphyrinatoiron(II) [T(piv)$_8$PP](1-hexylimidazole) (1979 cm^{-1}).[5a,d] This difference in ν(CO) for double-sided porphyrins is due to the electron-donating ability of the imidazole ligand. Since the imidazole coordination to the central iron of T(piv)$_8$PP was sterically restrained by the bulky pivaloyloxy groups, the electron donation from the axial base to the iron might be decreased compared to that in the single-face hindered series such as picket-fence porphyrinatoiron (TpivPP).[5d] On the other hand, the value of ν(CO) of **1b** was nearly the same to that of TpivPP, indicating that covalently attached imidazole of **1b** bound to the central iron(II) without the unfavorable steric repulsion on the rear side.

Kinetics of the O_2 binding were analyzed with laser flash photolysis of the O_2 adduct under CO binding competition by using Gibson's equation.[7,11] O_2 and CO binding affinity ($P_{1/2}(O_2)$, $P_{1/2}(CO)$: the pressure of O_2 or CO at half saturation; the reciprocal of the equilibrium constants)[12] of **1b** were 90 and 240 times higher than those of our previously reported 5,10,15,20-tetrakis(2,6-bis(3,3-dimethylbutyryloxy)phenyl)porphyrinato-iron ($T(db)_8PP$)/1,2-Me_2Im, respectively (Table 1).[5c,12] These porphyrinatoirons revealed gaseous ligand

Table 1. O_2 and CO binding parameters of porphyrinatoiron(II)s in toluene at 25 °C[a)]

Comlex	$k_{on}(O_2)$ / $dm^3mol^{-1}s^{-1}$	$k_{off}(O_2)$ / s^{-1}	$P_{1/2}(O_2)$ / Torr	$k_{on}(CO)$ / $dm^3mol^{-1}s^{-1}$	$k_{off}(CO)$ / s^{-1}	$P_{1/2}(CO)$ / Torr
1b	6.3×10^7	1.2×10^3	2.5	1.3×10^7	9.3×10^{-3}	7.2×10^{-5}
$T(piv)_35CImPP$[b)]	4.3×10^8	2.9×10^3	0.58	3.6×10^7	7.8×10^{-3}	2.2×10^{-5}
$T(db)_8PP$/1,2-Me_2Im[c)]	4.5×10^7	7.9×10^4	230	9.0×10^5	1.5×10^{-1}	1.7×10^{-2}

a) Estimated errors < 10%.
b) $T(piv)_35CIm$; Tailed picket-fence porphyrinatoiron(II). From Ref. 7.
c) 1,2-Me_2Im; 1,2-Dimethylimidazole. From Ref. 5c.

binding affinities of Relaxed(R) and Tense(T) state Hb.[6,7] The kinetic behaviors of O_2 and CO binding of **1b** corresponded to the R state.

In TpivPP, the pivalamide groups are believed to provide a distal moiety with a favorable electrostatic interaction with a coordinated dioxygen and contribute to an increasing of O_2 binding affinity.[1,7,8,11] In fact, the modified porphyrinatoirons with reversible O_2-coordinating capability often bear amide residues in their substituent groups on the porphyrin plane. The O_2 binding affinity of **1b** were slightly lower than that of tailed picket-fence heme ($T(piv)_35CImPP$),[7] which had a similar structure to **1b** except for containing an amide groups.

Our results show that the so-called amide effect[1,7,8,11] is not crucial for a reversible and stable dioxygen adduct if the porphyrin molecules is modified ingeniously.

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9) Spectroscopic data for **1a**: δ_H (400 MHz, $CDCl_3$, Me_4Si)-3.0(2H, s, inner H), -0.5-0.4(63H, m, t-butyl), 1.2(14H, m, -($C\underline{H}_2$)-), 2.8(2H, t, OC(=O)$C\underline{H}_2$-)), 6.1,6.7,6.8(3H, s, imidazole), 7.3-7.8(12H, m, phenyl), and 8.8(8H, s, pyrrole); *m/z* 1578 (M^+); λ_{max}($CHCl_3$) 654, 583, 536, 507, and 415 nm. **1b′**: *m/z* 1713 (M^+); λ_{max}($CHCl_3$) 680, 648, 582, 510, and 413 nm.

10) The phospholipid vesicle embedded with **1b** was prepared by sonication method as previously reported; E. Tsuchida, H. Nishide, M. Yuasa, E. Hasegawa, Y. Matsushita, and K. Eshima, *J. Chem. Soc., Dalton Trans.*, **1985**, 275. **1b**/DPPC=1/100 (molar ratio) in 30 mmol dm^{-3} phosphate buffer, pH 7.4.

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12) $P_{1/2}$(CO) was estimated by M value (K(CO)/K(O_2)), which was determined spectrophotometrically with flow method. Refs. 7,11.

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