

Double-Sided Porphyrinatoiron(II) Bearing Covalently Bound Imidazole.

An Efficient Oxygen-Carrier Molecule Composed by 8 Ester Bonds

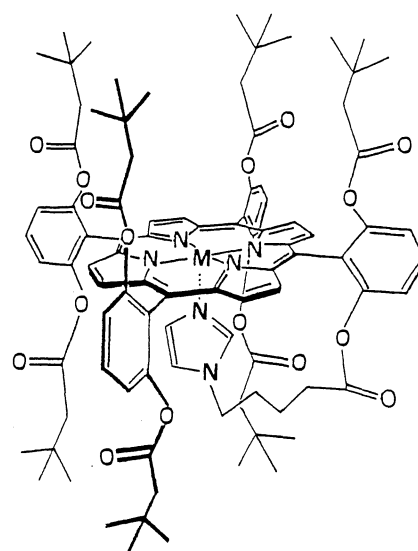
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Double-sided porphyrinatoiron(II) bearing covalently bound axial imidazole, 5,10,15-tris(2,6-bis(3,3-dimethylbutyryloxy)phenyl)-20-(2-(3,3-dimethylbutyryloxy)-6-(5-imidazolylvaleroyloxy)phenyl)porphyrinatoiron (**1b**), was synthesized: The substituents of **1b** are bound with the porphyrin only through ester bonds. **1b** formed a stable O₂ 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 O₂ 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 O₂ 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 O₂ 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 O₂



M;	2H	1a
	Fe ^{III} Br	1b'
	Fe ^{II}	1b

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 O₂ 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 O₂ 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 tetrahydrofuran (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 FeBr₂/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 Na₂S₂O₄ in a heterogeneous two-phase system under N₂ 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 O₂ adduct on exposure to O₂ (λ_{max} (toluene); 544 and 420 nm). The O₂ 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 O₂ adduct with respect to the irreversible oxidation of Fe(II) to Fe(III) in toluene at 25 °C was >2 days. Reversible O₂ 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 $\nu(\text{CO})$ 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)₈PP](1-hexylimidazole) (1979 cm⁻¹).^{5a,d)} This difference in $\nu(\text{CO})$ 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)₈PP 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 $\nu(\text{CO})$ 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 O₂ binding were analyzed with laser flash photolysis of the O₂ adduct under CO binding competition by using Gibson's equation.^{7,11)} O₂ and CO binding affinity (P_{1/2}(O₂), P_{1/2}(CO): the pressure of O₂ 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)porphyrinatoiron (T(db)₈PP)/1,2-Me₂Im, respectively (Table 1).^{5c,12)} These porphyrinatoirons revealed gaseous ligand

Table 1. O₂ and CO binding parameters of porphyrinatoiron(II)s in toluene at 25 °C^{a)}

Complex	$\frac{k_{on}(O_2)}{dm^3 mol^{-1} s^{-1}}$	$\frac{k_{off}(O_2)}{s^{-1}}$	$\frac{P_{1/2}(O_2)}{Torr}$	$\frac{k_{on}(CO)}{dm^3 mol^{-1} s^{-1}}$	$\frac{k_{off}(CO)}{s^{-1}}$	$\frac{P_{1/2}(CO)}{Torr}$
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) ₃ 5CImPP ^{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) ₈ PP/1,2-Me ₂ Im ^{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-Me₂Im; 1,2-Dimethylimidazole. From Ref. 5c.

binding affinities of Relaxed(R) and Tense(T) state Hb.^{6,7)} The kinetic behaviors of O₂ 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 O₂ binding affinity.^{1,7,8,11)} In fact, the modified porphyrinatoirons with reversible O₂-coordinating capability often bear amide residues in their substituent groups on the porphyrin plane. The O₂ 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, $-(\text{CH}_2)-$), 2.8(2H, t, $\text{OC}(=\text{O})\text{CH}_2-$), 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) $\text{P}_{1/2}(\text{CO})$ was estimated by M value ($\text{K}(\text{CO})/\text{K}(\text{O}_2)$), which was determined spectrophotometrically with flow method. Refs. 7, 11.

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