

Synthesis and Characterization of "Picnic-Basket" Porphyrins with a Substituent in the Interior of the Pocket

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"Picnic-basket" porphyrins of a new type, that have a substituent in the interior of the pocket, were synthesized to study stabilization of the bound oxygen in hemoprotein models. Though these Co(II) porphyrins have enormous equilibrium constants for the formation of base adducts, hydrogen-bonding interaction with coordinated dioxygen is not as effective for stabilization of the metal-dioxygen bond as we had expected. The results suggest that doming of the porphyrin plane plays an important role in the binding of dioxygen.

Keywords porphyrin; cobalt porphyrin; dioxygen carrier; ESR; synthesis; hydrogen-bonding; base-binding

Reversible binding of dioxygen to low-valent metalloporphyrins is interesting because it has relevance to the biological transport and activation of oxygen by hemoproteins.¹⁾ A large number of metalloporphyrins have been proposed as model compounds of hemoglobin.^{1a,2)} Stabilization of the bound O₂ by a hydrogen-bonding interaction with a nearby proton donor is known to occur.³⁾ For example, Chang and Kondylis reported that dioxygen binding to Co(II) 1-naphthyl porphyrins substituted with amido, carboxy, and hydroxymethyl groups at the 8-naphthyl position was significantly enhanced.^{3a)} The effects of amide groups in the vicinity of the oxygen-binding site in tetrakis(*o*-amidophenyl)porphyrinato derivatives were also reported.^{3b,d)} In this paper, synthesis and characterization of "picnic-basket" porphyrins of a new type (PBP, **5a—d**), which have both an *o*-amidophenyl superstructure and a hydrogen-bonding substituent in the interior of the pocket, are reported. Metalloporphyrins (**6c**, **6d**) derived from these ligands are expected to have a strong affinity for dioxygen because they have multiple hydrogen bond donors in the vicinity of the bound O₂ molecule. Other metalloporphyrins (**6a**, **6b**) which have only *o*-amidophenyl substituents were prepared for comparison with **6c** and **6d**. The pocket of these ligands does not have enough space for a base such as pyridine or 1-methylimidazole to form a σ -complex with the metal atom. The aim of this study was to estimate the ability of these proton donors to stabilize the dioxygen adduct.

Results

The ligands prepared here are specified by Collman's method,⁴⁾ *i.e.*, as Co(II) R-PBP, where R is a bridging group (MXY = *m*-xylene, DMB = 2,6-dimethylbenzoate, DMBAC = 2,6-dimethylbenzoic acid, and DMBAM = 2,6-dimethylbenzamide).

The synthesis of these porphyrins is shown in Chart 1. DMB-PBP (**5b**) was prepared by a reported procedure.⁵⁾ Potassium superoxide was used to convert **5b** to DMBAC-PBP (**5c**) because aqueous NaOH failed to hydrolyze the ester part of **5b** selectively. Preparation of DMBAM-PBP (**5d**) from **5c** by amidation failed because the chlorination of **5c** with SOCl₂ did not give the corresponding acid chloride. The amide group on the handle of **5d** must be prepared before the handle of the "picnic basket" is placed

on the porphyrin ring. The synthetic route to **5d** was essentially similar to that of **5b**, but the *tert*-butyl ester (**1c**) was used as a starting material. Refluxing CCl₄ containing **1c** and a catalytic amount of benzoyl peroxide in the presence of *N*-bromosuccinimide (NBS) gave *tert*-butyl 2,4-bis(bromomethyl)benzoate (**2c**). Etherification of the bromomethyl substituent with diethyl 5-hydroxyisophthalate gave *tert*-butyl 2,6-bis((3,5-diethoxycarbonylphenoxy)methyl)benzoate (**3c**). The *tert*-butyl ester part of **3c** was easily and selectively hydrolyzed with trifluoroacetic acid to give 2,6-bis((3,5-diethoxycarbonylphenoxy)methyl)benzoic acid (**3e**). The chlorination product formed from **3e** with SOCl₂ was condensed with NH₃ to give 2,6-bis((3,5-diethoxycarbonylphenoxy)methyl)benzamide (**3d**). The ethyl ester of **3d** was hydrolyzed with aqueous NaOH without hydrolysis of the amido group to give 2,6-bis((3,5-dicarboxyphenoxy)methyl)benzamide (**4d**). The chlorination product from **4d** with SOCl₂ was condensed with 4:0 atropisomer of $\alpha,\alpha,\alpha,\alpha$ -tetrakis(*o*-aminophenyl)porphyrin (TAPP) to give **5d**. The structures of **5a—d** were confirmed by NMR spectra and elemental analysis.

A typical example of changes in the visible spectrum during spectrophotometric titration of the porphyrins with nitrogenous bases is shown in Fig. 2. The absorption peak at 529 nm decreased with increasing concentration of pyridine. The presence of isosbestic points indicates that

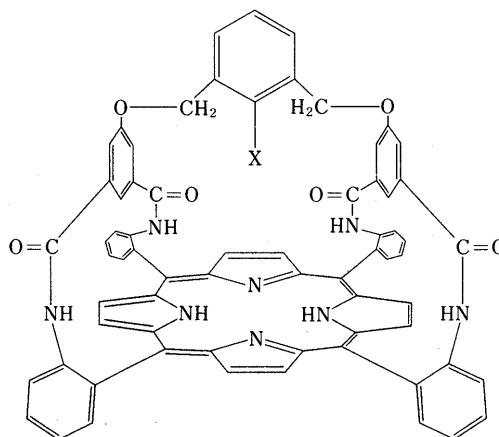


Fig. 1. Structure of "Picnic-Basket" Porphyrin

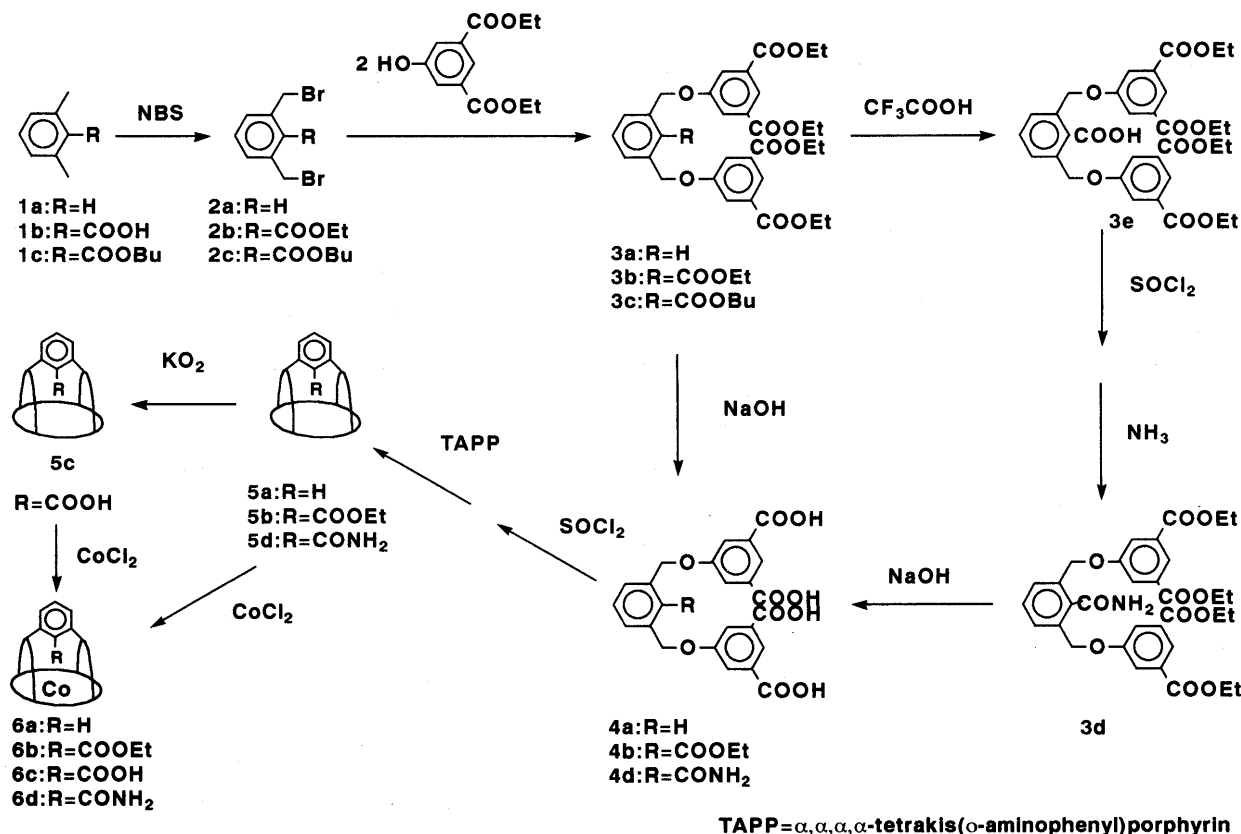


Chart 1

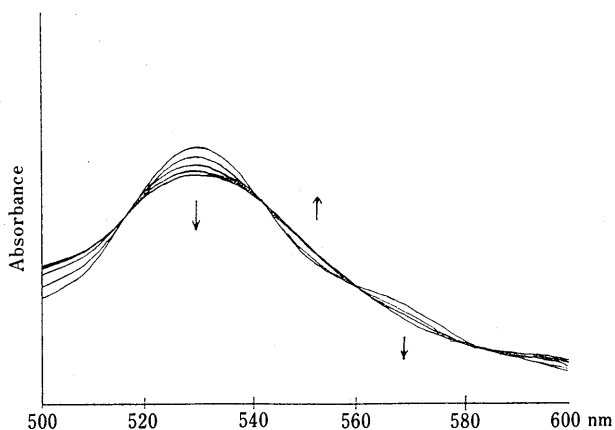


Fig. 2. Spectral Titration of Co(II) DMB-PBP (0.035 mM) with Pyridine (0.007–0.035 mM)

two chemical species are in equilibrium.

Analysis of the spectral changes gives the number of coordinated ligands (from the slope of the Hill plot) and the equilibrium constant (from the y -intercept of the Hill plot). In all cases 1 eq. of a base was bound; the equilibrium constants for the binding of bases are summarized in Table I.

The equilibrium constants for binding of 1-methylimidazole to **6b**, **6c** and **6d** are higher than those of pyridine. Compound **6b** gave the highest equilibrium constants for binding of 1-methylimidazole and pyridine. The equilibrium constant for binding of 1-methylimidazole to **6b** is 10^{11} times that of Co(II)-*T*(*p*-OMe)PP (**7**). The equilibrium constant for the base adduct of Co(II)MX-

TABLE I. Equilibrium Constants for Binding of Base to "Picnic-Basket" Porphyrins in Toluene at 25 °C

Compound No.	Porphyrin	1-Methylimidazole K_B, M^{-1}	Pyridine K_B, M^{-1}
6b	Co(II) DMB-PBP	2.2×10^{14}	4.4×10^9
6c	Co(II) DMBAC-PBP	4.8×10^5	3.5×10^2
6d	Co(II) DMBAM-PBP	8.2×10^5	^{a)}
7	Co(II) <i>T</i> (<i>p</i> -OMe)PP ^{b)}	2.3×10^3	4.9×10^2

^{a)} Hill's equation was not applicable. ^{b)} J. Almong, J. E. Baldwin, and J. Huff, *J. Am. Chem. Soc.*, **97**, 227 (1975). *T*(*p*-OMe)PP: $\alpha, \beta, \gamma, \delta$ -tetrakis(*p*-methoxyphenyl)porphyrin.

TABLE II. Equilibrium Constants for Dioxygen Binding to "Picnic-Basket" Porphyrins in Toluene

Compound No.	Porphyrin	1-Methylimidazole		Pyridine	
		-35 °C K_{O_2}, M^{-1}	-50 °C K_{O_2}, M^{-1}	-35 °C K_{O_2}, M^{-1}	-50 °C K_{O_2}, M^{-1}
6a	Co(II) MXY-PBP	1.4	6.7		
6b	Co(II) DMB-PBP	44	180	1.3 ^{a)}	4.4
6c	Co(II) DMBAC-PBP	31	140	0.5 ^{a)}	1.7
6d	Co(II) DMBAM-PBP	6.7	23	0.7 ^{a)}	2.0
7	Co(II) <i>T</i> (<i>p</i> -OMe)PP ^{b)}	310	1100	35	130

^{a)} Calculated from the thermodynamic data. ^{b)} J. Almong, J. E. Baldwin, and J. Huff, *J. Am. Chem. Soc.*, **97**, 227 (1975).

PBP (**6a**) was not obtained owing to the poor solubility of **6a** in toluene even in the presence of bases. Hill's equation does not hold between the spectral changes of the Co(II)DMBAM-PBP (**6d**) solution and the concentration of pyridine.

The equilibrium constants for dioxygen binding were

TABLE III. Thermodynamic Data for Dioxygen Binding of Co(II) "Picnic-Basket" Porphyrins in Toluene

Compound No.	Porphyrin	1-Methylimidazole		Pyridine	
		ΔH° (kcal/mol)	ΔS eu ^{a)}	ΔH° (kcal/mol)	ΔS eu ^{a)}
6a	Co(II) MXY-PBP	-5.3 ± 0.5	-20 ± 2		
6b	Co(II) DMB-PBP	-10.4 ± 1.0	-36 ± 4	-8.5 ± 0.1	-35 ± 0.4
6c	Co(II) DMBAC-PBP	-11.4 ± 1.2	-41 ± 5	-9.3 ± 0.7	-39 ± 3
6d	Co(II) DMBAM-PBP	-8.0 ± 0.2	-30 ± 0.5	-7.1 ± 0.1	-30 ± 0.2
7	Co(II) T(<i>p</i> -Me)PP ^{b)}	-8.9 ± 0.5	-26 ± 2	-9.3 ± 1.1	-32 ± 4
	Co(II) Tpivot ^{c)}	-12.2 ± 0.3	-38 ± 1	$-11.8 \pm 0.4^d)$	$-40 \pm 2^d)$

a) Standard state of 1 M O₂. The entropy units are cal·K⁻¹·mol⁻¹. b) From reference 6. c) From reference 3c; Tpivot: *meso*-tetrakis($\alpha,\alpha,\alpha,\alpha$ -*o*-pivalamidophenyl)porphyrin. d) 1,2-Dimethylimidazole was used instead of pyridine.

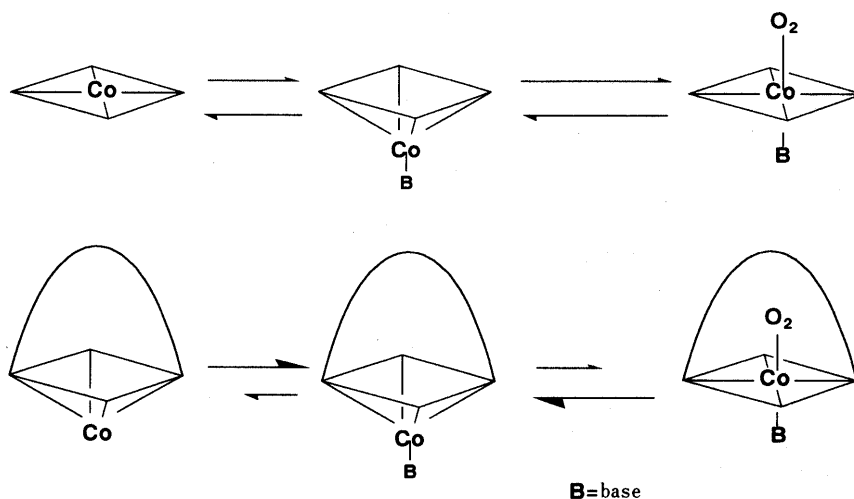


Chart 2

obtained by the method of Walker⁶⁾ and are summarized in Table II. The solubility of O₂ in toluene is approximately $7 \times 10^{-3} \text{ M} \cdot \text{atm}^{-1}$ at 25 °C, and is proportional to the O₂ pressure.⁷⁾

Though compound **6b** gave the highest equilibrium constant for O₂ binding, the equilibrium constants of **6a–d** are lower than that of **7**. The equilibrium constant of **6a** with O₂ in the presence of pyridine was not obtained owing to the poor solubility of **6a**.

Table III shows the enthalpies and entropies of the oxygenation equilibrium of the Co(II)porphyrin–base complex determined from van't Hoff plots, using data obtained at three different temperatures. Compound **6c** gave a large negative entropy which is consistent with the loss of rotational degree of freedom of the metal-bound O₂. The thermodynamic data for **6c** suggest the presence of hydrogen-bonding between the carboxylic proton and the coordinated dioxygen.

Discussion

Collman *et al.* reported an X-ray structure of Ru(C6-PBP)(CO)_{out}(Pyr)_{in}, one of the metallo picnic-basket porphyrins, and found that it accommodates a ligand base inside a pocket,^{5,8)} but examination of Corey-Pauling-Koltun (CPK) models shows that the pocket sizes of **5a–d** are not so large as that of C6-PBP. The bases in the five-coordinate cobalt porphyrins derived from Co(II)MXY-PBP (**6a**), Co(II)DMB-PBP (**6b**), Co(II)DMBA-PBP (**6c**), and Co(II)DMBAM-PBP (**6d**) must be outside the pocket

in the light of the following observations. Examination of CPK models shows that both 1-methylimidazole and pyridine are permitted to enter the pockets, but they are not able to form a σ -complex. The visible spectra of **6a–d** were changed even in the presence of a small amount of bases, as shown in Fig. 1. Walker reported that formation of π -complex caused no spectral change in the visible band.⁹⁾ These results support the above assumption.

Hydrogen-bonding to metal-bound dioxygen has been considered to be critical in directing the reaction course during oxygen activation. For effective hydrogen-bonding to take place, it is essential to minimize the distance and freedom of motion between the proton source and acceptor. As our synthetic target, therefore, we chose the "picnic-basket" porphyrin, which has a carboxylic proton in the pocket.

Contrary to our expectation, Co(II)DMBA-PBP-base did not show strong affinity to dioxygen in spite of exhibiting the expected hydrogen-bonding interaction between the carboxylic proton and coordinated dioxygen. A free energy gain of 1.3–1.1 kcal/mol for **6c** and **6d** with reference to **6a** at -42°C is comparable to that reported by Chang and Kondylis as evidence of the presence of a hydrogen bond.^{3a)} Although ΔH° of **6c** is lower than that of **7**, ΔS of the former is also lower than that of the latter. The accompanying loss in ΔS observed in **6c** is considered to be derived from loss of the rotational degree of freedom of the metal-bound O₂. This is one of the reasons why the affinity of **6c** for dioxygen is not so large. Another reason

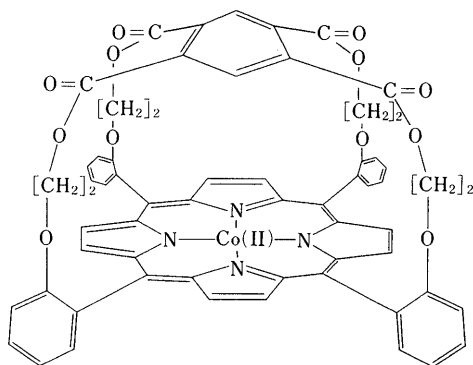


Fig. 3. Structure of Co(II) "Capped" Porphyrin

is doming, whose presence was suggested by high equilibrium constants for axial base binding. As shown in Chart 2, in the case of flat porphyrins, bases bind to metal in the porphyrin ring to pull it out of the ring plane, and O_2 binding to the metal pulls it back into the ring plane.¹⁰⁾

However, because of the considerable steric strain involved in attaching the picnic-basket handle of **6a—d**, the cobalt atom is considered to be displaced toward the other side of the pocket, which favors the coordination of bases. On the other hand, for the binding of dioxygen the metal must be pulled back to the porphyrin plane, which causes severe hindrance to the binding of dioxygen.

Table I shows that **6b—d** have large K_B . In contrast with **6b—d**, Co(II) capped porphyrins¹¹⁾ do not bind bases as strongly as does "flat" Co(II) porphyrin, 7.

The lower base affinity is not due to electronic effects because changes in the effects are known to have a relatively small effect on ligation of bases in these systems.¹¹⁾ Ellis *et al.* pointed out the following features to explain the lower base affinity of Co(II) capped porphyrins¹¹⁾: 1) the tetra-*meso*-phenyl groups are held rigidly in the plane in the Co(II) capped porphyrins; 2) pulling the metal out of the plane of the porphyrin toward the base is restricted in the metallo capped porphyrin. These considerations suggest that porphyrin plane of **6a—d** domes outside of the pocket, and that base adducts of **6a—d** are stable whereas the O_2 adducts of **6a—d** are not so stable. Possibly the interior substituents help to push the cobalt out of the porphyrin plane, because **6b**, which has the bulkiest substituent, has the largest K_B . The reason why **6b** has the largest K_{O_2} , though it does not have hydrogen-bonding ability, is that its bulky substituent does not permit the solvent (that is toluene) to enter the pocket, as is clear from the CPK model. Even when **6b** is distorted to allow the ethyl moiety of **6b** to escape from the "basket" cavity, the carbonyl moiety still remains in the cavity and occupies some space of the cavity.

Experimental

Apparatus Infrared (IR) spectra and 1H -NMR spectra were recorded on Hitachi 260-30 and Bruker AM-400 spectrometers. Chemical shifts are expressed in ppm downfield from $SiMe_4$ as an internal standard. Mass, UV and ESR spectra were obtained with Hitachi M-2000, Shimadzu UV-2100, and JEOL-FE1X spectrometers, respectively.

Materials Tetrahydrofuran (THF) was distilled after being refluxed over $LiAlH_4$ for 2 h. Carbon tetrachloride was refluxed for 1 h over CaH_2 followed by distillation. Dimethylformamide (DMF) was dried over molecular sieves, then distilled and stored over molecular sieves.

Dichloromethane was refluxed over CaH_2 for 5 h, then distilled. Toluene and benzene were each refluxed over CaH_2 for 4 h under an N_2 stream, then distilled under N_2 .

DMB-PBP (**5b**) was prepared by the reported procedure.⁵⁾

Co(II)DMB-PBP (6b) $CoCl_2$ (0.44 g) was added to a solution of THF (20 ml) containing **5b** (0.2 g) and a few drops of 2,6-lutidine, and the mixture was refluxed for 2 h under N_2 . After being passed through a column of the alumina (60 g), the reaction mixture was evaporated. The residue was recrystallized from $CHCl_3$ -MeOH to give **6b** (40 mg). *Anal.* Calcd for $C_{71}H_{48}CoN_8O_8 \cdot H_2O$: C, 70.00; H, 4.13. Found: C, 70.39; H, 4.17.

1,3-Bis(bromomethyl)benzene (**2a**): NBS (33 g) was added to a solution of *m*-xylene (9 ml) in CCl_4 (60 ml), and the mixture was stirred at room temperature for 3.5 h with a catalytic amount of benzoyl peroxide. The reaction mixture was filtered, and the filtrate was evaporated to dryness under reduced pressure. The residue was recrystallized from EtOH to give white crystals (**2a**) (5.4 g, 27.8%), mp 63–64°C. 1H -NMR ($CDCl_3$) δ : 4.42 (4H, s, CH_2), 6.59 (1H, s, aromatic proton), 7.26–7.55 (3H, m, aromatic proton). *MS* m/z : 261, 263, 265 (M^+), 183, 185 ($M^+ + 1 - Br$), 104 ($M^+ + 1 - 2Br$). *Anal.* Calcd for $C_8H_8Br_2$: C, 36.40; H, 3.05; Br, 60.54. Found: C, 35.85; H, 3.01; Br, 59.98.

1,3-Bis((3,5-diethoxycarbonylphenoxy)methyl)benzene (**3a**): Potassium carbonate (5 g) was added to a solution of **2a** (2.6 g) and diethyl 5-hydroxyisophthalate (4.6 g) in DMF (50 ml) and the mixture was stirred overnight. The reaction mixture was poured into $CHCl_3$ (150 ml) and washed with water (400 ml) once and then with water (100 ml) five times. The organic layer was dried over Na_2SO_4 and evaporated to dryness. The residue was recrystallized from EtOEt to give white crystals (5.2 g, 89.5%), mp 118–120°C. IR (KBr) cm^{-1} : 1725 (C=O). 1H -NMR ($CDCl_3$) δ : 1.14 (12H, t, $J=7.1$ Hz, CH_3), 4.40 (8H, q, $J=7.1$ Hz, O- CH_2), 5.17 (4H, s, CH_2), 7.44–7.45 (3H, m, aromatic proton), 7.56 (1H, s, aromatic proton), 7.84 (4H, d, $J=1.4$ Hz, aromatic proton), 8.29 (2H, t, $J=1.5$ Hz, aromatic proton). *MS* m/z : 578 (M^+), 533 ($M^+ - OEt$). *Anal.* Calcd for $C_{32}H_{34}O_{10}$: C, 66.42; H, 5.92. Found: C, 66.12; H, 5.89.

3-((3,5-Dicarboxyphenoxy)methyl)benzoyloxisophthalic Acid (**4a**): Compound **3a** (3.15 g) was dissolved in 95% EtOH (50 ml), and NaOH (1.25 g) in water (5 ml) was added. The solution was heated to 65°C, stirred overnight, and then filtered. The precipitate was washed with EtOH (100 ml) and dissolved in H_2O (150 ml). The aqueous solution was filtered, and concentrated hydrochloric acid (3 ml) was added to the filtrate. The precipitate was filtered off to give **4a** (1.58 g, 74%). IR (KBr) cm^{-1} : 3100 (COOH), 1700 (C=O). 1H -NMR ($CDCl_3$) δ : 4.87 (4H, s, CH_2), 6.93 (1H, s, aromatic proton), 7.21–7.23 (3H, m, aromatic proton), 7.26 (4H, d, $J=1.2$ Hz, aromatic proton), 7.62 (2H, t, $J=1.2$ Hz, aromatic proton). *Anal.* Calcd for $C_{24}H_{18}O_{10}$: C, 61.81; H, 3.89. Found: C, 61.58; H, 4.12.

MXY-PBP (**5a**): Compound **4a** (0.42 g) was refluxed overnight in $SOCl_2$ (5 ml) with a few drops of DMF. Excess $SOCl_2$ was evaporated off, then the residue was dissolved in CH_2Cl_2 and the solution was filtered. *n*-Hexane was added to the filtrate. The precipitate was collected by filtration and dried under reduced pressure to give an acid chloride. The acid chloride was dissolved in THF (50 ml) and added to a THF solution containing TAPP (600 mg) and triethylamine (0.5 ml) over a period of 2 h under an N_2 atmosphere, followed by stirring for 12 h. The reaction mixture was poured into $CHCl_3$ (200 ml) and washed with water (100 ml) three times. The organic layer was dried over Na_2SO_4 and evaporated to dryness. The residue was purified on a silica gel column using ether- CH_2Cl_2 (1:9) as an eluent to give **5a**. 1H -NMR ($CDCl_3$) δ : -2.67 (2H, s, inner H), 4.61 (4H, s, $-CH_2-$), 6.33 (1H, s, aromatic proton), 6.51 (2H, s, aromatic proton), 6.77 (4H, d, $J=1.4$ Hz, aromatic proton), 6.91–6.94 (3H, m, aromatic proton), 7.21 (4H, s, aromatic proton), 7.70 (4H, dt, $J=7.5, 1.2$ Hz, aromatic proton), 7.91 (2H, dt, $J=8.3, 1.4$ Hz, aromatic proton), 8.48 (2H, d, $J=8.3$ Hz, aromatic proton), 8.69 (4H, dd, $J=8.3, 1.0$ Hz, aromatic proton), 8.74 (4H, s, aromatic proton), 9.07 (4H, s, aromatic proton). *Anal.* Calcd for $C_{68}H_{46}N_8O_6 \cdot 2H_2O$: C, 73.76; H, 4.55; N, 10.12. Found: C, 73.33; H, 4.13; N, 9.99.

Co(II)MXY-PBP (6a) $CoCl_2$ (1.24 g) was added to a solution of THF (100 ml) containing MXY-PBP (0.12 g) and a few drops of 2,6-lutidine and the mixture was refluxed for 8 h. The reaction mixture was worked up by the same method as described for the preparation of **6b**. *Anal.* Calcd for $C_{68}H_{44}CoN_8O_6 \cdot 2H_2O$: C, 70.03; H, 4.32; N, 9.60. Found: C, 70.07; H, 4.13; N, 9.46.

DMBA-PBP (5c) Compound **5b** (1.5 g) and KO_2 (4.7 g) were added to 1.4% 18-crown-6 benzene solution (150 ml). The reaction mixture was

stirred overnight, refluxed for 3 h, and then poured dropwise into a separating funnel containing CH_2Cl_2 (250 ml) and H_2O (250 ml). After shaking, the organic layer was separated, washed with H_2O (200 ml) three times, dried over Na_2SO_4 , and evaporated. The residue was purified on a silica gel column using $\text{EtOH}-\text{CHCl}_3$ (1:20) as an eluent. Recrystallization from $\text{CHCl}_3-\text{MeOH}$ gave pure **5c** (0.56 g, 38%). $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ : -2.91 (2H, s, inner H), 4.75 (4H, s, CH_2), 6.47 (2H, s, aromatic H), 6.73 (4H, s, aromatic H), 6.99–7.00 (3H, m, aromatic H), 7.37 (4H, s, aromatic H), 7.75 (4H, t, $J=7.2$ Hz, aromatic H), 8.01 (4H, t, $J=7.3$ Hz, aromatic H), 8.46 (4H, d, $J=7.3$ Hz, aromatic H), 8.63 (4H, d, $J=7.3$ Hz, aromatic H), 8.85 (4H, s, pyrrole H), 9.01 (4H, s, pyrrole H). *Anal.* Calcd for $\text{C}_{69}\text{H}_{44}\text{N}_8\text{O}_8 \cdot \text{CH}_2\text{Cl}_2$: C, 70.18; H, 3.87; N, 9.35. Found: C, 70.47; H, 4.29; N, 9.32.

Co(II)DMBA-PBP (6c) CoCl_2 (0.22 g) was added to THF (10 ml) containing **5c** (0.1 g) and a drop of 2,6-lutidine, and the mixture was refluxed for 2.5 h. The reaction mixture was filtered and the filtrate was evaporated. The residue was recrystallized from $\text{CHCl}_3-\text{MeOH}$ to give **6c** (30 mg, 29%). *Anal.* Calcd for $\text{C}_{69}\text{H}_{42}\text{CoN}_8\text{O}_8 \cdot 3\text{H}_2\text{O}$: C, 67.70; H, 3.95; N, 9.15. Found: C, 67.72; H, 3.94; N, 9.10.

tert-Butyl 2,6-Dimethylbenzoate (1c) 2,6-Dimethylbenzoic acid (10 g) was stirred for 5 h in SOCl_2 (15 ml) containing 5 drops of DMF under N_2 gas. Excess SOCl_2 was evaporated and the residue was dissolved in CH_2Cl_2 (20 ml). This solution was added to a CH_2Cl_2 solution (20 ml) containing *tert*-butyl alcohol (12.6 ml) and the mixture was refluxed for 1 h. The solvent was evaporated off and the residue was purified by column chromatography using silica gel and benzene as an eluent to give **1c** (13.1 g, 95%). IR (KBr) cm^{-1} : 1725 (C=O). $^1\text{H-NMR}$ (CDCl_3) δ : 1.60 (9H, s, *tert*-Bu), 2.23 (6H, s, CH_3), 7.00 (2H, d, $J=7.7$ Hz, aromatic proton), 7.15 (1H, t, $J=7.7$ Hz, aromatic proton). *Anal.* Calcd for $\text{C}_{13}\text{H}_{18}\text{O}_2$: C, 75.69; H, 8.79. Found: C, 75.65; H, 9.04.

tert-Butyl 2,6-Bis(bromomethyl)benzoate (2c) NBS (25 g) and a catalytic amount of benzoyl peroxide were added to a CCl_4 solution containing **1c** (13.8 g) and the mixture was refluxed for 4 h. The reaction mixture was filtered and the filtrate was evaporated to give an oil. The product was crystallized by cooling the oil. The crystals were washed with hexane to give pure **2c** (14 g, 58%), mp 102–104°C. IR (KBr) cm^{-1} : 1710 (C=O). $^1\text{H-NMR}$ (CDCl_3) δ : 1.70 (9H, s, *tert*-Bu), 4.62 (4H, s, $-\text{CH}_2\text{Br}$), 7.33–7.36 (3H, m, aromatic proton). *Anal.* Calcd for $\text{C}_{13}\text{H}_{16}\text{Br}_2\text{O}_2$: C, 42.88; H, 4.42. Found: C, 42.99; H, 4.20. MS m/z : 362, 364, 366 (M^+).

tert-Butyl 2,6-Bis((3,5-Diethoxycarbonylphenoxy)methyl)benzoate (3c) Diethyl 5-hydroxyisophthalate⁵⁾ (5.3 g), **2c** (3.9 g) and K_2CO_3 (12.3 g) were added to dry DMF (80 ml) and the mixture was stirred overnight under an N_2 stream. The reaction mixture was poured into CH_2Cl_2 (150 ml) and the organic layer was washed with water (100–150 ml) 6 times, dried over Na_2SO_4 , and evaporated. The residue was collected and washed with ether to give **3c** (3.17 g, 43%), mp 176–177°C. IR (KBr) cm^{-1} : 1763 (C=O), 1722 (C=O), 1241 (C–O–C). $^1\text{H-NMR}$ (CDCl_3) δ : 1.41 (12H, t, $J=7.1$ Hz, $-\text{CH}_2\text{CH}_3$), 1.50 (9H, s, *tert*-Bu), 4.40 (8H, q, $J=7.1$ Hz, $-\text{CH}_2\text{CH}_3$), 5.29 (4H, s, $-\text{CH}_2-$), 7.45–7.57 (3H, m, aromatic proton), 7.82 (4H, d, $J=1.4$ Hz, aromatic proton), 8.31 (2H, t, $J=1.4$ Hz, aromatic proton).

2,6-Bis((3,5-diethoxycarbonylphenoxy)methyl)benzoic Acid (3e) Trifluoroacetic acid (34.9 ml) was added to a solution of CH_2Cl_2 (100 ml) containing **3c** (3.17 g), and the solution was stirred overnight. The reaction mixture was dissolved in CH_2Cl_2 (100 ml). The organic layer was washed with water (100 ml) 4 times and dried over Na_2SO_4 . The organic layer was removed to give a yellow oil which was crystallized with addition of ether. The crystals were washed with ether to give pure **3e** (2.4 g, 82%), mp 137–138°C. IR (KBr) cm^{-1} : 1721 (C=O), 1240 (C–O–C). $^1\text{H-NMR}$ (CDCl_3) δ : 1.40 (12H, t, $J=7.1$ Hz, $-\text{CH}_2\text{CH}_3$), 4.38 (8H, q, $J=7.1$ Hz, $-\text{CH}_2\text{CH}_3$), 5.34 (4H, s, $-\text{CH}_2-$), 7.49–7.56 (3H, m, aromatic proton), 7.60 (4H, d, $J=1.4$ Hz, aromatic proton), 8.27 (2H, t, $J=1.4$ Hz, aromatic proton). *Anal.* Calcd for $\text{C}_{33}\text{H}_{34}\text{O}_{12}$: C, 63.66; H, 5.50. Found: C, 63.39; H, 5.54.

2,6-Bis((3,5-diethoxycarbonylphenoxy)methyl)benzamide (3d) Compound **3e** (2.4 g) and a few drops of DMF were refluxed in SOCl_2 (33.4 ml) under N_2 gas overnight. Excess SOCl_2 was removed, and the residue was dissolved in sufficient amount of CH_2Cl_2 . Three times as much hexane as CH_2Cl_2 by volume was added to the solution. The resulting white precipitate was filtered off and dried under vacuum to give the acid chloride, which was dissolved in dry acetonitrile (100 ml). The acetonitrile solution was added dropwise to an aqueous NH_3 with stirring at below 15°C for 1 h. The reaction mixture was poured into ethyl acetate (100 ml) and the whole was washed twice with water

(100 ml). The organic solution was dried over Na_2SO_4 and evaporated. The residue was recrystallized from EtOH to give pure **3d** (1.5 g, 65%), mp 137–138°C. $^1\text{H-NMR}$ (CDCl_3) δ : 1.41 (12H, t, $J=7.1$ Hz, $-\text{CH}_2\text{CH}_3$), 4.40 (8H, q, $J=7.1$ Hz, $-\text{CH}_2\text{CH}_3$), 5.36 (4H, s, $-\text{CH}_2-$), 7.47–7.59 (3H, m, aromatic proton), 7.83 (4H, d, $J=1.4$ Hz, aromatic proton), 8.30 (2H, t, $J=1.3$ Hz, aromatic proton). *Anal.* Calcd for $\text{C}_{33}\text{H}_{35}\text{NO}_{11}$: C, 63.76; H, 5.67; N, 2.25. Found: C, 63.75; H, 5.44; N, 2.00. MS m/z : 622 (M^+).

2,6-Bis((3,5-dicarboxyphenoxy)methyl)benzamide (4d) Compound **3d** (2.1 g) was dissolved in 95% EtOH (32 ml), and aqueous NaOH (0.79 g in water (3 ml)) was added to the solution. The reaction mixture was heated to 65°C and stirred for 12 h, then cooled to room temperature and filtered. The precipitate was washed with EtOH (100 ml) and dissolved in water (95 ml). The solution was filtered and aqueous HCl was added to the filtrate. The precipitate was filtered off to give **4d** (1.15 g, 67%), mp 277–288°C (dec.). IR (KBr) cm^{-1} : 1660 (C=O). $^1\text{H-NMR}$ (D_2O) δ : 5.20 (4H, s, CH_2), 7.46 (1H, t, $J=7.2$ Hz, aromatic H), 7.55 (2H, d, $J=7.5$ Hz, aromatic H), 7.63 (4H, s, aromatic H), 8.08 (2H, s, aromatic H). *Anal.* Calcd for $\text{C}_{25}\text{H}_{19}\text{NO}_{11} \cdot \text{H}_2\text{O}$: C, 56.93; H, 4.01; N, 2.65. Found: C, 56.54; H, 3.95; N, 2.41.

DMBAM-PBP (5d) Compound **4d** (1.15 g), SOCl_2 (40 ml) and a few drops of DMF were refluxed overnight under an N_2 stream. Excess SOCl_2 was removed, the residue was dissolved in CH_2Cl_2 and the solution was filtered. The filtrate was evaporated to dryness to give acid chloride (1.17 g, 88%). The total amount of the acid chloride was dissolved in THF (70 ml) and this solution was added dropwise to THF (230 ml) containing TAPP (1.35 g) and triethylamine (1.1 ml) over a period of 2 h. The reaction mixture was stirred for another 12 h, then evaporated to dryness, and the residue was dissolved in CHCl_3 (100 ml). The CHCl_3 solution was washed with water (300 ml) 3 times and dried over Na_2SO_4 . The solvent was evaporated off and the residue was purified by column chromatography on silica gel using ether- CH_2Cl_2 (1:9) as an eluent to give **5d**, which was recrystallized from $\text{CHCl}_3-\text{MeOH}$ (0.7 g, 31%). $^1\text{H-NMR}$ (CDCl_3) δ : -2.93 (2H, s, inner H), 4.82 (4H, s, CH_2), 6.67 (2H, s, CH_2), 6.92 (4H, d, $J=1.2$ Hz, aromatic H), 6.99–7.01 (5H, m, aromatic H), 7.38 (4H, s, aromatic H), 7.69 (4H, dt, $J=7.5$, 1.0 Hz, aromatic H), 7.92 (4H, t, $J=8.0$ Hz, aromatic H), 8.44 (4H, dd, $J=7.5$, 1.4 Hz, aromatic H), 8.73 (4H, s, pyrrole H), 8.76 (4H, d, $J=8.1$ Hz, aromatic H), 9.06 (4H, s, pyrrole H). *Anal.* Calcd for $\text{C}_{69}\text{H}_{43}\text{N}_7\text{O}_7 \cdot 2\text{H}_2\text{O}$: C, 72.17; H, 4.30; N, 10.97. Found: C, 72.04; H, 3.79; N, 10.74.

Co(II)DMBAM-PBP (6d) CoCl_2 (0.2 g) was added to a solution of THF (10 ml) containing **5d** (0.1 g) and a drop of 2,6-lutidine, and the mixture was refluxed for 2 h. The reaction mixture was filtered and the filtrate was evaporated. The residue was recrystallized from $\text{CHCl}_3-\text{MeOH}$ (40 mg, 38%). *Anal.* Calcd for $\text{C}_{69}\text{H}_{43}\text{CoN}_7\text{O}_7 \cdot 2\text{H}_2\text{O}$: C, 68.66; H, 3.92; N, 10.44. Found: C, 68.79; H, 3.73; N, 10.64.

Base-Binding Measurement Equilibrium constants (K_B) for the binding of bases were obtained by a spectrophotometric titration method. Aliquots of deoxygenated base diluted with toluene were added to a toluene solution of the metalloporphyrin under N_2 in a 1-cm optical cell. The temperature of the porphyrin solution was controlled with Shimadzu CPS-260 to a precision of $\pm 0.5^\circ\text{C}$. Spectra were recorded in the range of 500–600 nm. A plot based on the Hill equation was drawn by the least-squares method to obtain K_B ;

$$\log y/(1-y) = \log [B] + \log K_B$$

where $y = (A_{\text{obsd}} - A_0)/(A_\infty - A_0)$ and A_{obsd} = absorbance at specific [B], A_0 = initial absorbance where [B] = 0, and A_∞ = final absorbance when the fully ligated porphyrin is the only species present.^{1,2)} Values for $\log K_B$ were obtained from the y intercept of the regression line for a plot of $\log y/(1-y)$ vs. $\log [B]$.

Dioxygen-Binding Measurement Equilibrium constants for the binding of dioxygen were determined by Walker's method.⁶⁾ A toluene solution containing equivalent amounts of metalloporphyrin and base was introduced into a quartz ESR tube equipped with a stopcock and degassed by two freeze-and-thaw cycles. A known pressure of O_2 (100–760 Torr) was introduced into the tube. The temperature was adjusted to a known value in the range of +5 to -80°C , as appropriate for the system under investigation. The derivative ESR spectrum was integrated to give the absorption spectrum. The ratio of dioxygen adduct (CoP-B-O_2) to five coordinate amine complex (Co-P-B) was estimated from $((\text{area of Co-B-O}_2 \text{ peak}) \times \langle g \rangle_{5\text{-coord}}) / ((\text{area of Co-B peak}) \times \langle g \rangle_{\text{dioxygen-adduct}})$. Areas were determined by the use of a planimeter. The g -value correction is necessary to account for magnetic susceptibility

differences in the two systems.

References and Notes

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