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Dioxygen Binding in Iron and Cobalt Picnic Basket Porphyrins

James P. Collman,* Xumu Zhang, Kelvin Wong, and John I. Brauman

Contribution from the Department of Chemistry, Stanford University,
Stanford, California 94305-5080

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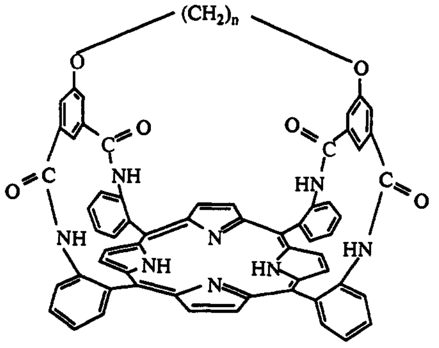
Abstract: The synthesis and characterization of a series of iron and cobalt "picnic basket" porphyrins are described. Dioxygen binding to iron and cobalt picnic basket porphyrins has been studied by ^{1}H NMR and oxygen affinity measurements. These iron and cobalt picnic basket porphyrins bind dioxygen reversibly at room temperature with high affinities. The oxygen affinity increases as the basket size decreases. This effect indicates that a dipole–dipole interaction between the terminally bound dioxygen and the amide protons may play a role in the stability of the oxygen adducts. ^{1}H NMR spectroscopy does not support the existence of a strong H-bond in these picnic basket porphyrins. Oxygen affinities of the cobalt picnic basket porphyrins are more sensitive to the change of basket sizes than are the corresponding iron porphyrins. This result is consistent with the idea that the $Co^{II}O_2$ adducts have more electron density on the oxygen ligand than do the $Fe^{II}O_2$ adducts.

Introduction

Over the past several decades, the nature of oxygen binding to myoglobin, hemoglobin, and synthetic model systems has been the subject of intensive research.[1] Of particular interest is the effect of "distal" groups on the O_2 affinities of different heme environments. In hemoglobin and myoglobin, various experiments show that H-bond or dipole–dipole interactions between the distal histidine and the terminal bound dioxygen play an important role in stabilizing the oxygen adducts.[2] Dipole–dipole or H-bond interactions have also been proposed in several biomimetic heme analogues. Notable examples are the "picket fence", "pocket", and "basket handle" porphyrin complexes.[3] Iron derivatives of these porphyrins bind dioxygen reversibly at room temperature with high affinities. For biomimetic studies of O_2 binding, stable FeO_2 adducts offer many advantages over unstable compounds. Such stability provides the possibility of obtaining X-ray diffraction crystal structures of the FeO_2 adducts and of measuring various spectroscopic properties.



C_nPBP n = 2, 4, 6, 8, 10

Figure 1. Picnic basket porphyrins.

In this paper we report a new, stable oxygen binding system involving iron and cobalt "picnic basket" porphyrins (Figure 1). The picnic basket porphyrins have a cavity of variable dimensions on one face of the porphyrin ring. The unhindered face of the porphyrin plane can be blocked by coordination of bulky axial ligands to the central metal. This situation forces the binding of dioxygen with the cavity of the basket superstructure which is on the opposite face. By changing the basket size, one can systematically examine the oxygen binding properties of these metalloporphyrins. Herein, we describe the synthesis and characterization of iron and cobalt picnic basket porphyrins. Oxygen affinities have been measured for iron and cobalt picnic basket porphyrins having different cavity sizes. In an attempt to understand the O_2 binding interactions in this system, we have studied ^{1}H NMR spectra of various free-base and metallo picnic basket porphyrins.

Results

Synthesis. The picnic basket porphyrins have been synthesized and characterized as described in the literature.[4] As shown in Scheme 1, a similar picnic basket porphyrin having a small cavity, half-C_2PBP, has been prepared. This synthesis is convergent; after chromatography, the yield of the final condensation is 26%. Metalation of these picnic basket porphyrins proceeds smoothly in high yield.

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(3) Abbreviations: MP, metalloporphyrin; B, nitrogenous base; $P_{1/2}O_2$, partial pressure of O_2 at half-saturation; K, equilibrium constant; Im, imidazole; 1-MeIm, 1-methylimidazole; 1,2-Me_2Im, 1,2-dimethylimidazole; 1,5-DCIm, 1,5-dicyclohexylimidazole; Mb, myoglobin; Hb, hemoglobin; TPP, dianion of *meso*-tetraphenylporphyrin; T(*p*-OCH_3)PP, dianion of *meso*-tetrakis(*p*-methoxyphenyl)porphyrin; PPIXDMe, dianion of protoporphyrin IX dimethyl ester; C_2-cap, dianion of "capped" 5,10,15,20-[pyromelitoyl(tetrakis(*o*-oxylethoxyphenyl))]porphyrin; TPivP, dianion of picket fence, *meso*-tetrakis-($\alpha,\alpha,\alpha,\alpha$-pivalamidophenyl)porphyrin; TTPPP, dianion of 5,10,15,20-tetrakis-(2,4,6-triphenyl)porphyrin; $Piv_3$5CIM, dianion of "tailed" picket fence, *meso*-tris(α,α,α-*o*-pivalamidophenyl)(β-*o*-(*N*-imidazolyl)valeramidophenyl)-porphyrin; PocPiv, dianion of "small" pocket, 5,10,15-(1,3,5-benzenetriacetyl)-tris(α,α,α-*o*-aminophenyl)-20-(α-*o*-pivalamidophenyl)porphyrin; MedPiv, dianion of "medium" pocket, 5,10,15-((1,3,5-benzenetripropionyl)tris(α,α,α-*o*-aminophenyl))-20-(α-*o*-pivalamidophenyl)porphyrin; AzP, dianion of 5,15-diphenyl-10,20-bis(α,α-nonanediamidodi-*o*-phenylene)porphyrin; bis-fenced P, dianion of 5,10,15,20-tetrakis(2,6-bis(pivaloyloxy)phenyl)porphyrin; 6,6-cyclophane and 7,7-cyclophane, see refs 27 and 30; amide-Py BHP (basket handle porphyrin) and ether-Py BHP, see ref 11; amide-Im BHP, see ref 33.

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Scheme 1

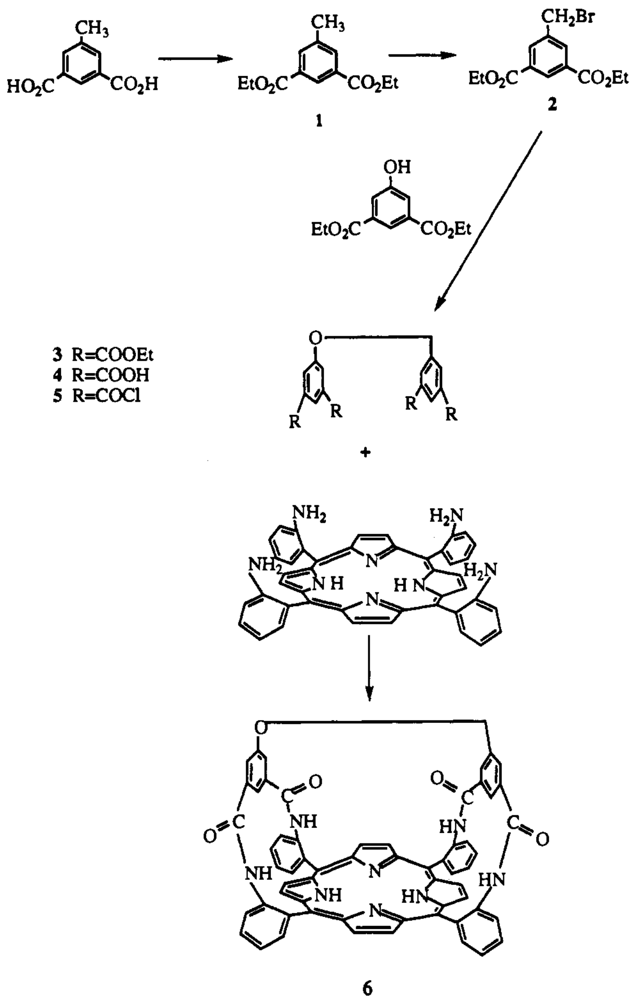

Table 1. ^{1}H NMR Data for Amide N-H of PBPs

porphyrin	chemical shift (ppm)	porphyrin	chemical shift (ppm)
half-C$_2$PBP	5.55, 5.51	C$_6$PBP	7.53
C$_2$PBP	6.28	C$_8$PBP	7.77
C$_4$PBP	7.06	C$_{10}$PBP	7.92

^{1}H NMR Spectroscopy. Each unmetalated picnic basket porphyrin has been characterized by ^{1}H NMR spectroscopy. The amide protons in these porphyrins have been assigned by D$_2$O exchange (Table 1). The diamagnetic O$_2$ and CO adducts as well as the paramagnetic five-coordinate complexes of the iron(II) picnic basket porphyrins have also been studied by ^{1}H NMR (Table 2). Note that Fe(II) porphyrins typically bind a second, unhindered axial ligand with a greater affinity than the first; this is explained by a spin change from $S = 2$ to $S = 0$. The half-C$_2$PBP and C$_2$PBP complexes give five-coordinate paramagnetic complexes with bulky imidazoles (1,5-DCIm, 1,2-Me$_2$Im) and stable, diamagnetic dioxygen complexes upon O$_2$ addition to these five-coordinate species. With 1,5-DCIm as the axial ligand, neither stable O$_2$ adducts nor solvent-free five-coordinate complexes can be made with the C$_4$PBP or C$_6$PBP derivatives, which have larger cavity sizes and do not exclude these axial ligands. When 1,2-Me$_2$Im serves as the axial ligand, it binds inside the larger cavities of C$_4$PBP and C$_6$PBP; this hindered ligand typically gives 1:1 complexes even with unhindered Fe(II) porphyrins.

O$_2$ Affinity Studies. Equilibrium O$_2$ binding affinities of the metalated picnic basket porphyrins have been measured with a tonometer. Before the gas titration, sufficiently high concentrations of imidazoles (100–1000 equiv) were added to ensure that the five-coordinate complex is the predominant form in solution. All of these experiments satisfied two criteria: adequate isosbestic behavior was maintained during the course of O$_2$ gas titration and the $P_{1/2}$O$_2$ values were shown to be independent of the axial base concentration. When bulky 1,5-DCIm was used to block the open face of the metalated picnic basket porphyrins, it gave an R-state (high-affinity) model of hemoglobin. Conversely, when 1,2-Me$_2$Im was used to block the open face, it gave a T-state (low-affinity) model of hemoglobin. The $P_{1/2}$O$_2$ values of the Fe(II) and Co(II) porphyrin complexes are listed in Tables 3 and 4, respectively. A typical example of dioxygen binding data is shown in Figure 2. Inconclusive data were obtained in the following cases: Fe(C$_6$PBP) and Co(C$_6$PBP) with 1,5-DCIm; Fe(C$_4$PBP), Fe(C$_6$PBP), Co(C$_4$PBP), and Co(C$_6$PBP) with 1,2-Me$_2$Im. With 1,5-DCIm as the ligand, oxygen affinity measurements of Fe(C$_4$PBP) did not give satisfactory isosbestic points; however, an estimate of $P_{1/2}$O$_2$ (1773 Torr) was obtained with a large error ($2\sigma = 551$ Torr). The other measured $P_{1/2}$O$_2$ values are reproducible within ±15% using a range of different base concentrations.

Table 2. ^{1}H NMR Data for Five-Coordinate Complexes, O$_2$, and CO Adducts of Iron(II) Picnic Basket Porphyrins

porphyrin	β-pyrrole proton (ppm)	amide proton (ppm)
Fe(half-C$_2$PBP)(1,5-DCIm)	58.27, 58.22, 57.09, 56.94	
Fe(O$_2$)(half-C$_2$PBP)(1,5-DCIm)	8.40, 8.36, 8.35–8.31	5.75, 5.48
Fe(CO)(half-C$_2$PBP)(1,5-DCIm)	8.91, 8.89, 8.31, 8.26	5.62
Fe(half-C$_2$PBP)(1,2-Me$_2$Im)	55.82, 56.65, 54.43, 54.35	
Fe(O$_2$)(half-C$_2$PBP)(1,2-Me$_2$Im)	8.42–8.30	5.79, 5.50
Fe(CO)(half-C$_2$PBP)(1,2-Me$_2$Im)	8.92, 8.90, 8.31, 8.26	5.56
Fe(C$_2$PBP)(1,5-DCIm)	59.11, 57.73	
Fe(O$_2$)(C$_2$PBP)(1,5-DCIm)	8.27, 8.02	6.19
Fe(CO)(C$_2$PBP)(1,5-DCIm)	8.85, 8.37	6.21
Fe(C$_2$PBP)(1,2-Me$_2$Im)	58.86, 53.94	
Fe(O$_2$)(C$_2$PBP)(1,2-Me$_2$Im)	*a*	6.29
Fe(CO)(C$_2$PBP)(1,2-Me$_2$Im)	8.95, 8.47	6.22

[a] The chemical shifts were not assigned due to the overlap of NMR peaks.

Table 3. O$_2$ Binding of Iron(II) Porphyrin Complexes to R-State and T-State Models of Hemoglobins at 25 °C

system	$P_{1/2}$O$_2$ (Torr)	physical state	ref
	R State		
Mb	0.70	pH 8.5	25
Hb, human	0.15–1.5	various	26
chelated protoheme	5.6	benzene (20 °C)	27
FePiv$_3$5CIm	0.58	toluene	28
FePocPiv(1-MeIm)	0.36	toluene	24, 29
FeMedPoc(1-MeIm)	0.36	toluene	24, 29
6,6-cyclophane(1,5-DCIm)	696	benzene (20 °C)	27
7,7-cyclophane(1,5-DCIm)	1.4	benzene	30
Fe(C$_2$-cap)(1-MeIm)	23	toluene	31
FeTPivPP(1-MeIm)	0.49	solid	32
Fe(amide-Im BHP)	0.29	toluene	33
Fe(amide-Py BHP)	2.0	toluene	11
Fe(ether-Py BHP)	18	toluene	11
Fe(bis-fenced P)	56	toluene	9
Fe(half-C$_2$PBP)(1,5-DCIm)	0.28	toluene	this work
Fe(C$_2$PBP)(1,5-DCIm)	0.35	toluene	this work
	T State		
Hb, human	9–160	various	26
FeTPP(2-MeIm)	140	toluene	34
FeTPivPP(1,2-Me$_2$Im)	38	toluene	28
FePocPiv(1,2-Me$_2$Im)	12.6	toluene	24
FeMedPoc(1,2-Me$_2$Im)	12.4	toluene	24
FeTalPoc(1,2-Me$_2$Im)	4	toluene	24
Fe(C$_2$-cap)(1,2-Me$_2$Im)	4000	toluene	31
Fe(AzP)(1,2-Me$_2$Im)	27	toluene	18
Fe(TTPPP)(1,2-Me$_2$Im)	508	toluene	8
Fe(half-C$_2$PBP)(1,2-Me$_2$Im)	14	toluene	this work
Fe(C$_2$PBP)(1,2-Me$_2$Im)	25	toluene	this work

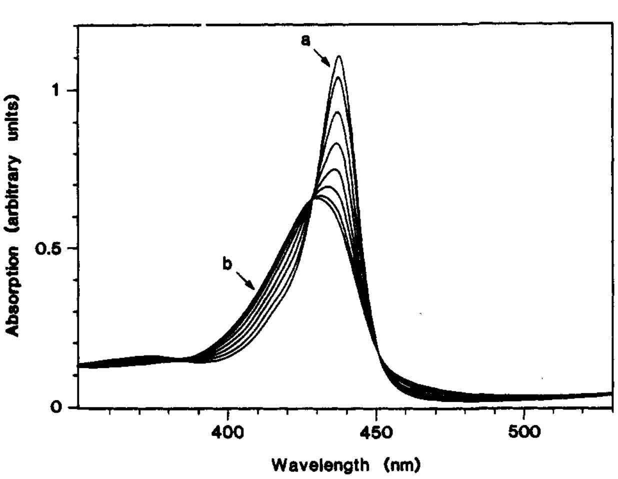

Figure 2. Determination of $P_{1/2}O_2$ for Fe(C_2PPBP)(1,2-Me_2Im). Ca. 1×10^{-5} M porphyrin in toluene with 1 mM 1,2-Me_2Im, 25.0 °C: (a) under 1 atm of N_2; (b) under O_2 partial pressure of 94.18 Torr. The following intermediate partial pressures of O_2 were used: 2.97, 8.73, 17.39, 28.80, 45.64, and 67.59 Torr.

Table 4. O_2 Binding of Cobalt(II) Porphyrin Complexes to R-State and T-State Models of Hemoglobins at 25 °C

system	$P_{1/2}O_2$ (Torr)	physical state	ref
	R State		
CoMb (sperm whale)	57	0.1 M phosphate, pH 7	34
CoMb (horse)	57	0.1 M phosphate, pH 7	35
CoMb (sperm whale)	50	0.1 M phosphate, pH 7	36
CoTPivPP(1-MeIm)	61	solid	38
CoTPivPP(1-MeIm)	140	toluene (20 °C)	28
CoT(*p*-OCH_3)PP(1-MeIm)	15 500	toluene	38
CoPPIXDME(1-MeIm)	17 800	toluene	38
CoPPIXDME(1-MeIm)	11 000	toluene	38
Co(half-C_2PBP)(1,5-DCIm)	7	toluene	this work
Co(C_2PBP)(1,5-DCIm)	25	toluene	this work
Co(C_4PBP)(1,5-DCIm)	278	toluene	this work
Co(bis-fenced P)(1-MeIm)	136	CH_2Cl_2 (–66 °C)	9
	T state		
CoHb	160	0.1 M phosphate, pH 7.4 (15 °C)	26
CoTPivPP(1,2-Me_2Im)	900	toluene	38
Co(AzP)(1,2-Me_2Im)	278	toluene	18
Co(half-C_2PBP)(1,2-Me_2Im)	99	toluene	this work
Co(C_2PBP)(1,2-Me_2Im)	208	toluene	this work

Discussion

Dipole–dipole or H-bonding interactions have a strong influence on the oxygen affinities of synthetic heme analogues. Some iron porphyrins with different polarities in their oxygen binding pockets are shown in Figure 3. Dipole–dipole or H-bonding interactions have been proposed to play an important role in stabilizing O_2 adducts of iron picket fence porphyrins. The picket fence porphyrin has four amide protons directed toward the porphyrin center.[5] An X-ray structure of the iron dioxygen complex reveals that the amide N to terminal O atom distances vary from 3.88 to 4.14 Å.[6] These distances are about 1 Å longer than a normal H-bond. Nevertheless, it has been suggested that a weak H-bond or a strong dipole–dipole interaction is critical in stabilizing this O_2 adduct.[7] When nonpolar *o*-phenyl groups are incorporated in the porphyrin (e.g., a bis-pocket porphyrin[8] or an ester-substituted bis-picket fence porhyrin[9]), the oxygen affinity decreases dramatically. For example, the $P_{1/2}O_2$ value of Fe(bis-fenced P)(1-MeIm) is 56 Torr, while the $P_{1/2}O_2$ of FeTPivPP(1-MeIm) in the solid state is 0.49 Torr; $P_{1/2}O_2$ is 508 Torr for Fe(TTPPP)(1,2-Me_2Im) and 38 Torr for FeTPivPP(1,2-Me_2Im). When one of four pivalamide pickets is replaced by a substituent capable of a stronger H-bonding interaction in this picket-fence porphyrin, the oxygen affinity increases. For example, a 10-fold increase in oxygen affinity was observed with a phenylurea substituent.[10]

Dipole–dipole or H-bonding interactions are also important factors in controlling oxygen affinities of the basket handle porphyrins. The basket handle porphyrins have amide groups near the binding site of the O_2 molecule; these could affect an intramolecular H-bonding interaction between the amide proton and the terminal oxygen atom. A nearly 10-fold higher O_2 affinity was observed for an amide-linked basket handle porphyrin (Fe(amide-Py BHP), $P_{1/2}O_2$ = 2.0 Torr) compared to its ether-linked analogue (Fe(ester-Py BHP), $P_{1/2}O_2$ = 18 Torr).[11] ^{1}H NMR,[12] ^{17}O NMR,[13] IR,[14] and resonance Raman[15] spectra have been used to probe for H-bonding interactions in this system.

Oxygen affinity studies have shown that O_2 affinity is significantly enhanced in cobalt naphthylporphyrins substituted with groups which are capable of H-bonding.[16] EPR has been employed to study H-bonding between an *o*-acetamide derivative of cobalt tetraphenylporphyrin and bound dioxygen.[17] Other systems related to H-bond or dipole–dipole interactions include jellyfish-type porphyrin,[18] amide-containing cyclophane heme,[19] and tailed hemes with appended polar groups.[20] In addition, small amounts of H-bonding solvents have been shown to enhance the O_2 affinity of metal complexes.[21]

Because both dipole–dipole and H-bonding interactions can strongly affect the O_2 affinities, it would be interesting to have a system in which the oxygen binding properties could be specifically correlated with these interactions. Previously we reported a convergent synthesis of picnic basket porphyrins. Unlike the picket fence porphyrin, the amide N–H of picnic basket porphyrins can be forced toward the porphyrin center by decreasing the basket size. When the amide N–H is close enough to the porphyrin center in these iron and cobalt porphyrins, we might expect strong dipole–dipole interactions and possibly a H-bond could occur between the amide and bound dioxygen. As a result, these metalloporphyrins may form kinetically more stable dioxygen adducts and bind dioxygen with higher equilibrium affinities (Figure 4). In the present study, we have prepared a smaller picnic basket porphyrin (half-C_2PBP) and compared O_2 binding affinities of both its Fe(II) and Co(II) derivatives with those of the larger basket porphyrins: C_2PBP, C_4PBP, and C_6PBP.

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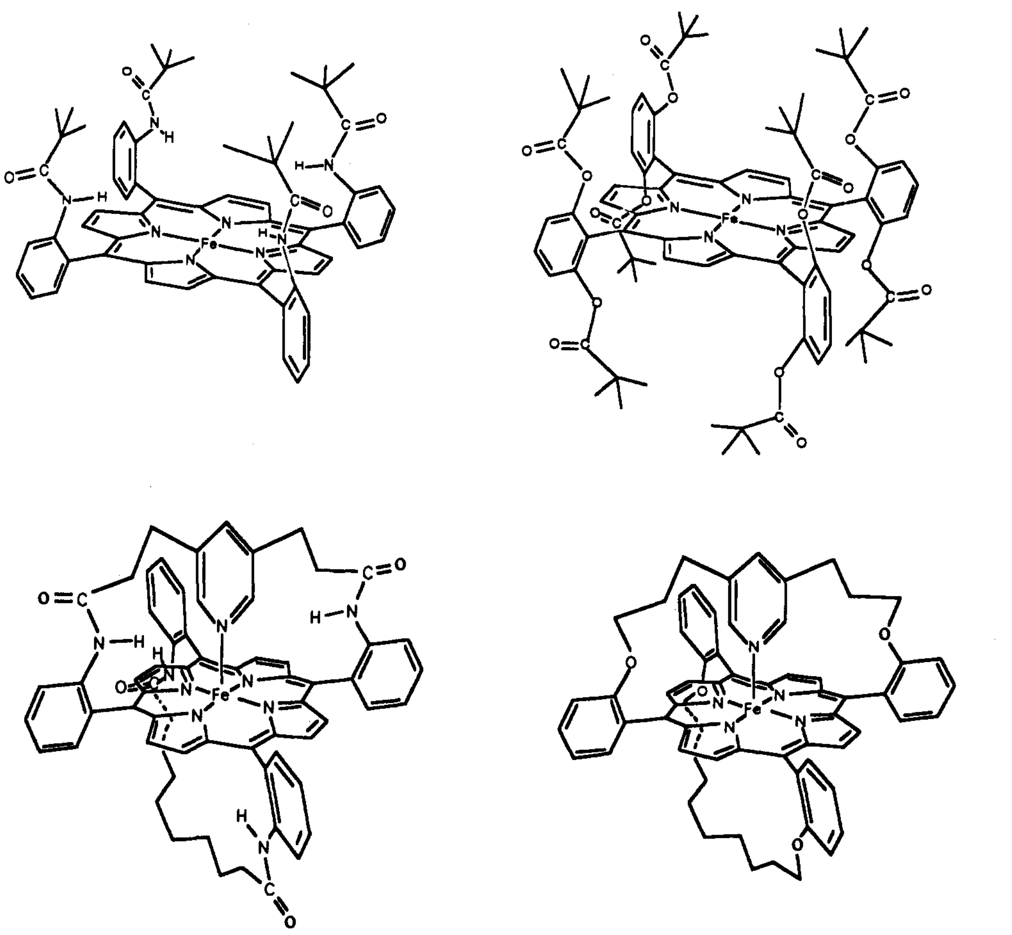

Figure 3. Some representative iron porphyrins with different polarities in their oxygen binding pockets. (Top left) Fe(TPivPP), picket fence porphyrin. (Top right) Fe(bis-fenced P). (Bottom left) Fe(amide-Py BHP). (Bottom right) Fe(ether-Py BHP).

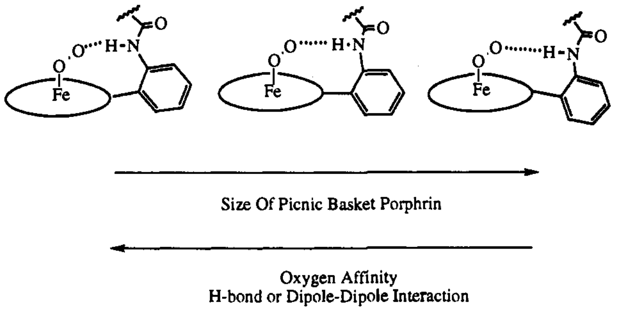

Figure 4. Correlation of oxygen affinity *vs* the basket size.

^{1}H NMR Spectroscopy. ^{1}H NMR spectral data for the picnic basket porphyrins are listed in Table 1. The chemical shifts of the amide protons move upfield with decreasing basket size, presumably due to porphyrin ring current effect. Differences of chemical shifts as large as 2.5 ppm are manifest between baskets of different size.

The ^{1}H NMR spectra of Fe(II) picnic basket porphyrins provide insight into the structural properties of the metalloporphyrins. Five-coordinate iron porphyrin complexes with axial bases give paramagnetic contact-shifted NMR spectra, whereas O_2 and CO adducts give diamagnetic spectra.[22] It is notable that these Fe–O_2 adducts are sufficiently stable at room temperature to give clean, diamagnetic ^{1}H NMR spectra. In addition, ^{1}H NMR studies of basket handle porphyrins have been used to probe for possible H-bonding interactions between an amide NH and the terminal oxygen of the dioxygen complexes. If H-bonding interactions exist in this system, the O_2 adducts should have low-field-shifted amide proton resonances compared to the corresponding CO adducts.[12] The ^{1}H NMR data in Table 2 show that the chemical shift values of the amide protons in O_2 and CO adducts of the iron C_2PBP complex are about the same. These results indicate that an H-bonding interaction is probably not present in this system; a strong dipole–dipole interaction presumably contributes to the high O_2 affinity in the iron C_2PBP complex. On the other hand, the chemical shifts of amide protons in O_2 and CO adducts of the iron half-C_2PBP exhibit some differences (Table 2). With the CO adducts, the two sets of amide protons have similar chemical shifts. However, with the O_2 adducts, the two sets of amide protons are separated by about 0.28 ppm. This subtle difference could be explained as follows: dioxygen binds to the iron porphyrin in a bent mode, which causes the dioxygen dipole to have a preferred orientation toward one set of amide protons. In contrast, CO binds to the iron in a linear fashion; consequently, the dipole of CO exerts an equivalent influence on the chemical shift of all amide protons. Compared to published reports where the differences of chemical shifts between O_2 and CO adducts are more than 1 ppm,[12] the differences of chemical shifts reported here are not large enough to support the presence of a H-bonding interaction in the present system.

O_2 Affinity Studies. In order to bind dioxygen within the picnic basket porphyrin cavity, the open face of the porphyrin must be effectively blocked by an axial ligand. This can be achieved by providing a sufficiently high concentration of coordinating base, while the superstructure of the picnic basket porphyrin prevents the base from binding inside the pocket. For these oxygen

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equilibrium measurements, five-coordinate porphyrin complexes are required, and the oxygen binding site has to be sterically hindered so as to prevent formation of μ-dioxygen bridged complexes between two metalloporphyrins. In this study, we have used two types of imidazoles: 1,5-dicyclohexylimidazole (1,5-DCIm) and 1,2-dimethylimidazole (1,2-Me_2Im). Nonbonded repulsive interactions between the methyl group on the 2-methylimidazole and the electrons of the porphyrin ring result in lengthened axial bonds, including the Fe–O bond in the dioxygen adduct.[23] As a result, the oxygen affinity with a 2-methylimidazole axial base is lower than that obtained with an imidazole which has a H atom at the 2-position. Porphyrins bonded to imidazoles which have a methyl group at the 2-position have been suggested as "T-state" models of hemoglobin (the low-affinity form); porphyrins coordinated by imidazoles with a H atom at the 2-position have been used as "R-state" models of hemoglobin (the high-affinity form).[1k,24] We could not obtain oxygen affinity data on picnic basket porphyrins which are the same size as C6PBP or are larger. This is because the superstructure cavity is too large to prevent imidazole bases and solvents from binding inside the cavity. Even with C_4PBP, the only reliable result was obtained with the cobalt porphyrin coordinated to a bulky imidazole (1,5-dicyclohexylimidazole). Tables 3 and 4 summarize O_2 binding constants for these Fe(II), Co(II) picnic basket porphyrins and other metalloporphyrins. In general, the oxygen affinities of Fe(II) and Co(II) picnic basket porphyrins are comparable to those obtained with the picket fence, pocket, and basket handle porphyrins. These porphyrins are all derived from the tetrakis(*o*-aminophenyl)porphyrin and have similar ortho amide groups on the porphyrins. Compared with sterically unencumbered porphyrins such as TPP, PPIXDME, and chelated protoheme, the oxygen affinities of the picnic basket porphyrins are substantially higher. These dramatic variations in O_2 affinities may result from several factors such as the electronic and structural nature of the porphyrin, solvation effects, and especially the polarity of the dioxygen binding site. It is often difficult to distinguish the relative importance of these factors in the control of dioxygen affinities. On the other hand, compared with the oxygen affinities of the nonpolar sterically protected heme models such as TTPPP, bis-fenced P, and C_2-cap, the polarity of the O_2 binding site in the picnic basket porphyrins seems to be the dominant factor in accounting for the high oxygen affinities. As we have demonstrated here, the polarity of the picnic basket porphyrins has been investigated by systematically varying the basket size. In both Fe(II) and Co(II) picnic basket porphyrins, there is a clear trend of O_2 affinities with different basket sizes.

With the half-C_2PBP and C_4PBP, the oxygen affinity of the Fe(II) complexes is 1.4–2.7-fold higher than that in the picket fence porphyrin in both R- and T-state models. This suggests that in these porphyrins, stronger interactions occur between the amide group and the bound dioxygen. The oxygen affinity of iron basket handle porphyrin (amide-Im BHP)[12] and jellyfish porphyrin (AzP),[18] in which the H-bond between the amide proton and the terminal oxygen has been demonstrated by ^{1}H NMR, is comparable to the oxygen affinity of the half-C_2PBP iron derivatives. This raises the question of whether a weak H-bonding interaction is present in the half-C_2PBP derivative.

With the cobalt picnic basket porphyrins, the parallel between oxygen affinity and the size of the cavity is more pronounced than it is in the corresponding iron porphyrins. The oxygen affinity of the Co half-C_2PBP is more than 20-fold greater in the R-state model than that of Co picket fence porphyrin and 9-fold greater in the T-state model. As the basket size decreases from C_4PBP to C_2PBP, and further to half-C_2PBP, the $P_{1/2}O_2$ decreases from 278 to 25 and 7 Torr, respectively. This change in O_2 affinity with change in basket size is more pronounced in the Co porphyrins than in the Fe porphyrins. This different response can be explained as follows: the $Co^{II}O_2$ adducts have more electron density in the oxygen ligand compared with the $Fe^{II}O_2$ adducts. Consequently, electrostatic interactions between the amide groups and the CoO_2 species are more sensitive to changes in polarity than are the corresponding FeO_2 species. This hypothesis is in agreement with a theoretical analysis.[7] This theoretical calculation indicates that there is more negative charge located in the bound dioxygen in the CoO_2 adducts than in the corresponding FeO_2 adducts.

Conclusions

We have synthesized a series of iron and cobalt picnic basket porphyrins. High oxygen affinities have been observed with the small picnic basket porphyrins, and the oxygen affinities have been found to decrease dramatically as the basket size increases. This effect demonstrates that either a dipole–dipole or a H-bonding interaction between the terminally bound dioxygen and the amide protons influences the oxygen affinity in these metalloporphyrins. ^{1}H NMR spectroscopy does not show any indication of a H-bond within the small pockets of these porphyrins. Comparison of these oxygen affinities indicates that electrostatic interactions between the amide groups of PBP and the CoO_2 species are more sensitive to the change of basket sizes than are those of the corresponding FeO_2 species; this is consistent with proposals that the CoO_2 adducts have more electron density in the O_2 ligand than do the FeO_2 adducts.

Experimental Section

Materials. Iron dibromide (Strem), cobalt dibromide (Aldrich), and 1,5-dicyclohexylimidazole (Aldrich) were used as received. Solvents were distilled under a nitrogen atmosphere. Methylene chloride was distilled from P_2O_5. Methanol was dried and distilled from $Mg(OMe)_2$. Benzene, diethyl ether, tetrahydrofuran, and toluene were distilled from sodium benzophenone ketyl. Dry DMF was obtained by reduced pressure distillation from BaO. Thionyl chloride was distilled from triphenyl phosphite. 2,6-Lutidine was stored over KOH and distilled from BaO. 1,2-Dimethylimidazole was distilled from KOH. Silica gel manufactured by E. M. Science (Type 7736) was used for flash chromatography.

^{1}H NMR Measurements. ^{1}H NMR spectra were obtained on a Nicolet NMC-300 or Varian XL-400 spectrometer and referenced to the residual proton signals of the deuterated solvents. Fe(II) porphyrin NMR samples were prepared as follows: to an Fe(II) porphyrin, freshly prepared by metalation in a glovebox ($O_2 < 1$ ppm), were added $CDCl_3$ and imidazoles (4–10 equiv), and the five-coordinate Fe(II) complexes were identified by their characteristic paramagnetic contact-shifted NMR spectra. These solutions were exposed to an atmosphere of O_2 or CO at room temperature. Spectra of the O_2 and CO adducts were obtained at room temperature. Amide protons of the porphyrins were identified by deuterium exchange with D_2O.

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Equilibrium Measurements. O_2 affinities were measured spectrophotometrically with a Hewlett-Packard 8452A diode array spectrometer with a 7470A plotter. The temperature of the UV–vis cell was regulated at 25 ± 0.02 °C with a B. Braun Thermomix 1480 immersion thermostat and a Frigomix 1480 automatic circulating liquid bath. Measurements were made on toluene solutions in a 1-cm cuvette equipped with a 100-mL tonometer. The tonometer was sealed with an Ace thread (Ace Glass, Vineland, NJ) and a Teflon septum.

The equilibrium between the metalloporphyrin (MP) with an axial base (B) and O_2 can be expressed as follows:

$$\mathrm{MP} + \mathrm{B} \overset{K_1}{\rightleftharpoons} \mathrm{MP{\cdot}B}$$

$$\mathrm{MP{\cdot}B} \overset{K_2}{\rightleftharpoons} \mathrm{MP{\cdot}B{\cdot}O_2}$$

$$\mathrm{MP{\cdot}B} + \mathrm{B} \overset{K_3}{\rightleftharpoons} \mathrm{MP{\cdot}B_2}$$

Measurements were done with excess quantities of imidazole ligands (B) in order to maintain the five-coordinate complex MP·B as the dominant form. The basket structures blocked the formation of six-coordinate $\mathrm{MP{\cdot}B_2}$ ($K_3 = 0$). The relationship between the partial pressure of dioxygen and the equilibrium constant K_2 can be written as follows:[38,39]

$$pO_2 = [\mathrm{MB}]_t b\Delta\epsilon(pO_2/\Delta A) - 1/K_2$$

where pO_2 is the partial pressure of dioxygen, K_2 is the equilibrium constant of dioxygen binding as noted above, $[\mathrm{MB}]_t$ is the total metalloporphyrin concentration, b is the pathlength of the cell, $\Delta\epsilon$ is the difference in the molar extinction coefficients between the oxygenated and deoxygenated forms, and ΔA is the absorption difference between the absorption of the solution at pO_2 and in the absence of dioxygen. By plotting pO_2 vs $pO_2/\Delta A$, a straight line is obtained with an intercept of $-1/K_2$.

Since K_2 is the equilibrium constant of oxygen binding:

$$K_2 = [\mathrm{MP{\cdot}B{\cdot}O_2}]/[\mathrm{MP{\cdot}B}]pO_2$$

When the metalloporphyrin is half-oxygenated:

$$[\mathrm{MP{\cdot}B{\cdot}O_2}] = [\mathrm{MP{\cdot}B}]$$

Then:

$$1/K_2 = P_{1/2}O_2$$

The partial pressure of oxygen at which 50% of metalloporphyrin sites are bound with O_2 is defined as $P_{1/2}O_2$.

Using a gas-tight syringe, a known volume of gas is removed from the tonometer, and the same volume of dioxygen is then injected. The partial pressure of dioxygen in the tonometer which was calculated for each point, n, has a relationship with the partial pressure of the previous point, $n - 1$:

$$P_n\,(\mathrm{Torr}) = [P_{n-1}(V - v) + 760v]/V$$

where V is the volume of the tonometer which does not include the solution volume, v is the volume of the gas removed and oxygen added, and the total pressure is constant at 760 Torr.

In a general procedure, known amounts of O_2 or 2.00% O_2 in N_2 (Matheson) were injected into the tonometer through a gas-tight syringe. After the addition of each aliquot, the sample was shaken until the system reached equilibrium (~5 min). The absorbance spectra were measured in the region between 350 and 700 nm. An adequate concentration of porphyrin was applied so that the Soret absorption of each porphyrin was in the region of 0.7–1.5. Sets (7–8) of spectra were recorded for a range of oxygen partial pressures, and those spectra with isosbestic points were used to calculate equilibrium constants for oxygen binding. Absorbance values in the calculation were taken from the Soret maximum. Linear plots and least-squares analyses were carried out using RS/1 (BBN Software Products Corp.).

Synthesis. *meso*-Tetrakis(*o*-aminophenyl)porphyrin,[40] diethyl 5-hydroxylisophthalate,[41] and a series of picnic basket porphyrins (H_2C_nPBP, n = 2, 4, 6, 8, 10)[4] were prepared by published methods. The $\alpha,\alpha,\alpha,\alpha$ atropisomer was enriched by the silica gel reflux process.[42,43]

Diethyl 5-Methylisophthalate (1). 5-Methylisophthalic acid (34 g, 188.7 mmol) in absolute ethanol (250 mL) was placed in a 500-mL round-bottom flask fitted with a N_2 inlet, condensor, and gas dispersion tube. With stirring under a N_2 atmosphere, HCl gas was slowly bubbled into the solution through the gas dispersion tube for 20 min. The solution was stirred an additional 2 h and then poured into H_2O (300 mL). The mixture was extracted with CH_2Cl_2 (2 × 150 mL). The CH_2Cl_2 layer was washed with H_2O (3 × 150 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness under vacuum. The oily product was cooled in a freezer at −20 °C overnight, and a yellowish solid was obtained (36.6 g, 82%).

^{1}H NMR ($CDCl_3$): δ 8.47 (s, 1H), 8.03 (s, 2H), 4.39 (q, J = 7.1 Hz, 4 H), 2.44 (s, 3H), 1.40 (t, J = 7.1 Hz, 6H).

Diethyl 5-Bromomethylisophthalate (2). A 250-mL round-bottom flask was charged with diethyl 5-methylisophthalate (**1**) (8 g, 33.9 mmol), *N*-bromosuccinimide (6 g, 33.7 mmol), benzoyl peroxide (50 mg), and CCl_4 (100 mL). The mixture was heated at reflux for 24 h, cooled to room temperature, and filtered. The filtrate was concentrated under reduced pressure to about 20 mL; upon cooling to −20 °C, crude product precipitated. Purified product was obtained after recrystallization from 5% Et_2O/hexane (5.5 g, 51.5%).

^{1}H NMR ($CDCl_3$): δ 8.61 (s, 1H), 8.24 (s, 2H), 4.55 (s, 2H), 4.42 (q, J = 7.1 Hz, 4H), 1.42 (t, J = 7.1 Hz, 6H).

The Tetraester (3). Diethyl 5-bromomethylisophthalate (**2**) (5.12 g, 16.2 mmol), diethyl 5-hydroxylisophthalate (4.4 g, 18.5 mmol), K_2CO_3 (5 g), and dry DMF (50 mL) were placed in a 100-mL round-bottom flask under a N_2 atmosphere. The reaction mixture was stirred at room temperature. Progress of the reaction was monitored by TLC (SiO_2, CH_2Cl_2); it was complete after 12 h. The product mixture was poured into H_2O (300 mL), and the aqueous solution was extracted with CH_2Cl_2 (2 × 150 mL). The combined CH_2Cl_2 layer was washed with saturated $NaHCO_3$ (100 mL) and 5% NaOH (50 mL), dried over Na_2SO_4, filtered, and evaporated on a rotary evaporator to give the product (7.41 g, 96.5%).

^{1}H NMR ($CDCl_3$): δ 8.67 (s, 1H), 8.33 (s, 3H), 7.85 (s, 2H), 5.22 (s, 2H), 4.42 (m, 8H), 1.43 (m, 12H). MS: m/e = 472 M^+ for $C_{25}H_{28}O_9$ (LREI/CI). Anal. Calcd for $C_{25}H_{28}O_9$: C, 63.55; H, 5.97. Found: C, 63.26; H, 5.90.

The Tetraacid (4). The tetraester (**3**) (7.4 g, 15.7 mmol) was added to 95% EtOH (100 mL) in a 250-mL round-bottom flask fitted with a magnetic stirrer, heating mantle, and condenser. After the mixture was heated to 55 °C, a solution of NaOH (5 g) in H_2O (5 mL) was added. The mixture was allowed to react for 12 h, cooled to room temperature, and filtered. The white precipitate was washed once with ethanol (25 mL) and then dissolved in H_2O (300 mL). The aqueous solution was treated with 6 N HCl to precipitate the acid. The product was obtained by filtration, washed with H_2O, and dried at 80 °C under vacuum (5.6 g, 99.2%).

^{1}H NMR (D_2O/K_2CO_3): δ 8.12 (s, 1H), 7.94 (s, 2H), 7.70 (s, 1H), 7.49 (s, 2H), 5.15 (s, 2H).

The Tetraacid Chloride (5). The tetraacid (**4**) (5 g, 13.9 mmol), thionyl chloride (20 mL), and a drop of DMF were added to a 50-mL round-bottom flask under a N_2 atmosphere. The mixture was heated at reflux for 6 h until all of the solid dissolved. The excess $SOCl_2$ was removed under vacuum to give the product as a light tan solid (5.2 g, 86.3%).

^{1}H NMR ($CDCl_3$): δ 8.87 (s, 1H), 8.55 (s, 1H), 8.52 (s, 2H), 8.02 (s, 2H), 5.34 (s, 2H).

Half-C_2PBP (6). The reaction was run under rigorously dry conditions. All glassware was dried in a hot oven at 120 °C and cooled in the antechamber of a glovebox. $\alpha,\alpha,\alpha,\alpha$-Tetra(*o*-aminophenyl)porphyrin (2.74 g, 4.1 mmol) was dissolved in CH_2Cl_2 (200 mL) and stirred with 4-Å molecular sieve pellets (5 g) for 3 h in the glovebox. The acid chloride (**5**) (1.71 g, 4.1 mmol) was dissolved in CH_2Cl_2 (200 mL) in a flask. A 2-L three-neck round-bottom flask containing triethylamine (5 mL) and CH_2Cl_2 (800 mL) was fitted with a N_2 inlet and two 250-mL constant dropping funnels (Kontes). The porphyrin and acid chloride solutions were transferred by cannula into the funnels, respectively. At the same rate, the two reactants were added dropwise into the three-neck flask at 0 °C under a N_2 atmosphere. After 4 h, the addition was complete, and

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the solution was stirred an additional 24 h at room temperature. The CH_2Cl_2 solution was reduced to 300 mL, washed once with saturated $NaHCO_3$ (100 mL) and NaCl solution (100 mL), dried over Na_2SO_4, filtered, and evaporated to dryness. The residue was loaded onto a silica gel flash column prepared from a CH_2Cl_2 slurry and eluted from 20% acetone/CH_2Cl_2 to give the desired product (1.01 g, 25.8%).

^1H NMR ($CDCl_3$): δ 9.02 (s, 2H), 8.98 (s, 2H), 8.71 (m, 8H), 8.26 (d, *J* = 8.1 Hz, 2H), 8.17 (d, *J* = 8.0 Hz, 2H), 7.87 (m, 4H), 7.77 (m, 4H), 6.62 (s, 2H), 6.09 (s, 2H), 5.78 (s, 1H), 5.57 (s, 2H) D_2O exchangeable, 5.50 (s, 2H) D_2O exchangeable, 5.34 (s, 1H), 4.52 (s, 2H), −3.13 (s, 2H). MS: $m/z = 963$ $(M + H)^+$ for $C_{61}H_{38}N_8O_5$ (LSIMS$^+$). UV–vis (CH_2Cl_2): λ 405 (sh), 424 (Soret), 518, 550 (sh), 590, 644 nm. Anal. Calcd for $C_{61}H_{38}N_8O_5{\cdot}CH_2Cl_2$: C, 71.06; H, 3.85; N, 10.69. Found: C, 71.15, H, 4.04; N, 10.42.

Iron Insertion.[44] In a typical reaction, porphyrin (40 mg) and 2,6-lutidine (0.2 mL) were added to a boiling solution of benzene and tetrahydrofuran (20 mL, 1:1) in a glovebox. The oxygen concentration of the glovebox was continually monitored and maintained at less than 1 ppm. Anhydrous $FeBr_2$ (100 mg) was added, and the reaction mixture was heated at reflux for about 30 min until the reaction was complete as indicated by UV–vis spectroscopy. The solvents were evaporated under vacuum; the residue was redissolved in tetrahydrofuran/benzene (1:10) and loaded onto an alumina column (activity 1 neutral Al_2O_3, Woelm, 1 cm × 10 cm). The product was eluted with methanol/tetrahydrofuran/benzene (1:1:10) and condensed as a lyophilized solid. The metalation proceeds nearly quantitatively.

Cobalt Insertion.[28] Typical insertion conditions are as follows. A solution of porphyrin (40 mg), anhydrous $CoCl_2$ (100 mg), and 2,6-lutidine (0.2 mL) in THF (20 mL) was heated under reflux under a N_2 atmosphere. The reaction was monitored by UV–vis spectroscopy and was complete after 2 h. The THF was removed under vacuum, and the remaining solid was dissolved in benzene (50 mL). The benzene solution was washed with dilute ammonia solution (3 × 30 mL), dried with Na_2SO_4, filtered, and evaporated to dryness. The residue was loaded on a silica gel column, and the product was eluted with acetone/methylene chloride (1:5). The excess solvents were removed to give the product in 82–95% yield.

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