VOLUME 32 NUMBER 6
ACCOUNTS of CHEMICAL RESEARCH®
JUNE 1999

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Synthetic Models for Hemoglobin and Myoglobin

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Received December 4, 1997

Biological Dioxygen Carriers

(1) Myoglobin and Hemoglobin. Dioxygen (O_2) binds to certain coordinatively unsaturated transition metal ions, forming O_2 complexes. Biological dioxygen carriers are reversible O_2 complexes in which the extent of binding depends on temperature, partial pressure of oxygen, and pH.

Myoglobin (Mb) and hemoglobin (Hb) are the most common reversible O_2 binders in biological systems; they are responsible for the storage and transport of O_2 in most aerobic organisms. Myoglobin and hemoglobin are structurally similar. Myoglobin contains one heme prosthetic group; hemoglobin consists of four Mb-like subunits ($2\alpha + 2\beta$), each containing one heme prosthetic group.

Myoglobin stores O_2 in muscles to permit short bursts of metabolism at rates much greater than those which would be allowed by circulatory oxygen transport. In its native deoxy form (Figure 1), the ferrous ion of the heme is in a five-coordinate high-spin state ($S = 2$), with the imidazole group (His 93) serving as the axial ligand on the proximal side. Myoglobin reversibly binds molecular oxygen in the sixth, distal, vacant coordination site. Distal amino acid residues (e.g., His 64) control the immediate environment. They can induce polar, hydrophobic, or steric interactions which help regulate the affinities of the bound ligands.

Hemoglobin, on the other hand, transports O_2 in blood and adjusts binding affinity to various conditions required for appropriate uptake and release of O_2 through a series of allosteric interactions.[1,2] Through the "allosteric effect", the subsequent gas binding affinity of Hb is made greater in the presence of O_2 or carbon monoxide (CO) than in their absence. Myoglobin, having only one heme site per protein, shows no such effect.

(2) Control of Ligand-Binding Thermodynamics. Evidence to date suggests that the amino acid residues on the distal porphyrin face are capable of stabilizing the oxygen adduct while destabilizing the competing complex derived from binding of the endogenous toxic ligand CO.[3] Studies have shown that, in the absence of the globin protein, imidazole-ligated heme has a CO affinity much greater than that of the protein-bound heme, indicating that the protein plays a role in decreasing CO affinity.[4]

The most significant distal effect invoked in the stabilization of O_2 in Hb is the hydrogen-bonding interaction between coordinated O_2 and the distal histidine, which was initially proposed by Pauling.[5] Subsequent experiments have provided evidence for H-bonding of iron-bound dioxygen with the distal histidine.[6−10] A unique Hb from the bloodworm *Ascaris* (shown in Figure 2) has a remarkably high affinity for O_2, nearly 10^4 times that of mammalian Hb.[11,12] The origin of this high O_2 affinity is believed to be (1) a strong H-bond between tyrosine (Tyr

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10.1021/ar9603064 CCC: $18.00 © 1999 American Chemical Society
Published on Web 02/12/1999

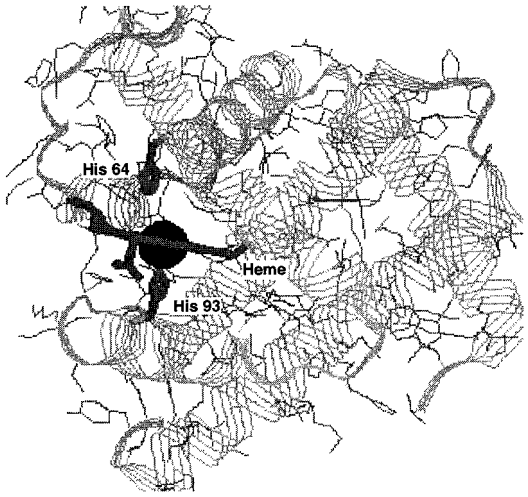

FIGURE 1. Crystal structure of deoxymyoglobin.

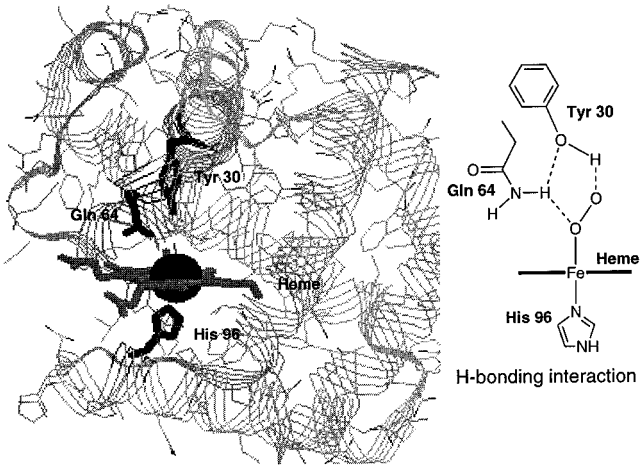

FIGURE 2. Crystal structure of oxyhemoglobin in bloodworm *Ascaris*.

30) and the terminal oxygen atom, (2) a weak H-bond between glutamine (Gln 64) and the oxygen atom bound to the heme iron, and (3) a third H-bond between these two amino acids.[13,14]

In addition to molecular oxygen, a variety of other small ligands are also able to bind to the sixth coordination site of the heme iron.[15−18] The *in vivo* degradation of heme, for example, generates exactly one molecule of CO per heme catabolized (in fact, approximately 1% of a human's hemoglobin is carbonylated due to this *in vivo* CO production[3]), resulting in a partial pressure of CO on the order of 10^{-3} Torr at the cellular level.[19] This endogenous toxic ligand binds heme Fe(II) tenaciously and thus severely inhibits hemoprotein's function.[1,20−24] Hemoproteins are clearly designed by nature to transport and store O_2 in the presence of the endogenous poison, CO. *M* values in the range of 100 are typical for Hb and Mb. (The relative binding affinity of CO versus O_2, referred to as the *M* value, is a useful measure of a complex's susceptibility to poisoning by CO. $M = P_{1/2}{}^{O_2}/P_{1/2}{}^{CO}$, where $P_{1/2}$ is the partial pressure of O_2 or CO at half-saturation. Thus, a lower *M* value denotes a higher affinity for O_2 relative to CO.)

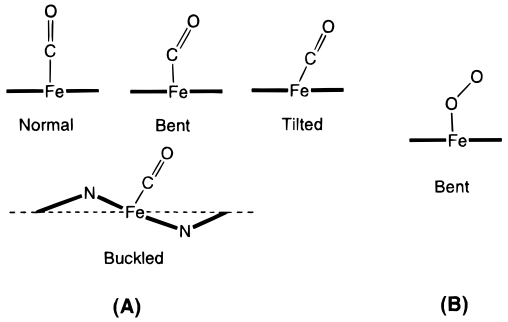

FIGURE 3. Structures of CO- and O_2-bound iron porphyrins.

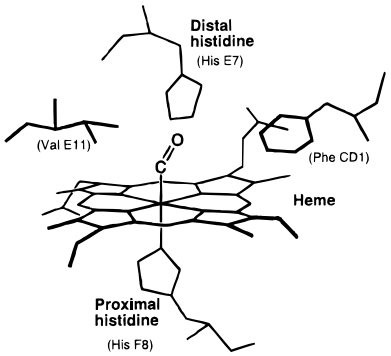

FIGURE 4. Destabilization of CO in hemoglobin and myoglobin.

In an unhindered environment, CO binds to heme iron at an angle orthogonal to the porphyrin plane as outlined in Figure 3A. In contrast, O_2 is bound in an intrinsically bent fashion at an angle of ∼120° (Figure 3B). The coordinated CO is expected to be much less polar, whereas the coordinated superoxide ion is polar, having a partial negative charge on the terminal oxygen atom. Both steric and polar effects in the distal region can affect the CO and O_2 binding affinities. Various distal groups have been shown to affect the protein's *M* value.[25−27]

(3) Some Controversial Issues. X-ray crystallographic studies of CO-bound Hb and Mb provide evidence of steric interactions between bound CO and protein residues as shown in Figure 4. The CO unit has been reported to be tipped off-axis, relative to the heme normal plane, from 7° to 47°.[28−35] This conflicts with evidence from vibrational spectroscopy which indicates a nearly upright FeCO geometry.[36,37] Recent *ab initio* calculations, based on density functional theory (DFT), indicate that the distortion potential is not as great as originally thought, and that modest protein forces could push the CO off-axis either via tilting or via bending.[38−41] Spiro *et al.*, using gradient-corrected DFT and full vibrational analysis, estimate that the energy requirement for a 0.9 Å off-axis displacement, produced by a 9° bend and 14° tilt, may be as little as 2 kcal/mol. Spiro and co-workers also point out that even if the CO is tilted from the normal to the porphyrin ring, the transition moment remains almost normal to the ring. This has important implications for optical selection experiments that suggest that the CO tilt angle is almost zero. They conclude that the energy cost for the distortions reported by crystallography no longer seems excessive.[40,41] Sage also suggests that distortion of the surrounding protein to accommodate the heme−CO

Table 1. Gas Binding Data for Compounds from the Literature[a]

	$P_{1/2}^{O_2}$ (Torr)	$P_{1/2}^{CO}$ (Torr)	M ($P_{1/2}^{O_2}/P_{1/2}^{CO}$)
	Proteins		
Hb (T-State) a[a]	40	0.3	135
Hb (T-State) b[a]	140	0.3	460
Hb (R-State)[a]	0.22	1.4×10^{-3}	150
Mb[a]	0.37−1	0.014−0.025	20−40
Ascaris[b]	0.002	0.1	0.02
	T-State Heme Models		
Fe (picket fence) (1,2-Me_2Im)[c]	38	8.9×10^{-3}	4280
Fe (TACN-capped) (1,2-Me_2Im)[c]	2.3	2.9	0.79
Fe (cyclam-capped) (1,2-Me_2Im)[c]	22	>3500	<0.006
Fe (cyclen-capped) (1,2-Me_2Im)[c]	760	>3500	<0.22
Fe (G1) (1,2-Me_2Im)[c]	0.035	0.35	0.10
Fe (G2) (1,2-Me_2Im)[c]	0.016	0.19	0.08
	R-State Heme Models		
Fe (4-atom-linked cap) (1-MeIm)[c]	280	100	2.8
Fe (TACN-capped) (1,5-DCIm)[c]	<0.2		
Fe (cyclam-capped) (1,5-DCIm)[c]	~ 3	>3500	<0.003
Fe (cyclen-capped) (1,5-DCIm)[c]	~ 760	>3500	<0.22

[a] $P_{1/2}$ values were measured under the following conditions: (a) H_2O, pH 7, 25 °C; (b) H_2O, pH 7, 20 °C; (c) toluene, pH 7, 25 °C. Note that changing the solvent polarity may slightly affect gas binding affinities.

complex may contribute significantly to the free energy of CO binding.[42,43]

The presence of water molecules in the binding pocket has also been suggested as contributing to the relative O_2 and CO affinities, known as the water-displacement model.[32,44] On the basis of their site-directed mutagensis of amino acids E7, E11, CD1, and B10, and kinetic measurements of rate constants for O_2 and CO binding,[32,45,46] the authors suggest that the equilibrium binding process requires the displacement of the distal pocket water molecule found in the native deoxymyoglobin and is enhanced when the water is absent due to replacement of the distal His E7 with apolar residues, e.g., Leu E7. (This seems a specious argument since relative equilibrium binding of O_2 *vs* CO involves removal of H_2O in both cases.) These authors also mention that it is still difficult to quantitate the relative importance of direct steric hindrance and electrostatic effects on CO binding to native myoglobin. Jameson further analyzes the O_2 and CO binding of these mutants, using the discrimination factor, the M value, and points out that the correlation of factors stabilizing O_2 binding and destabilizing CO binding is weak.[47]

On the other hand, comparison of thermodynamically and kinetically derived equilibrium constants should be made with caution.[27,48,49] It has been tacitly assumed that equilibrium constants for CO and O_2 binding, determined kinetically as the ratio k_{on}/k_{off}, are equivalent to those measured thermodynamically. Recent work however suggests that these may differ by as much as a factor of 5.[27,50] The reaction $Mb + O_2 \leftrightarrow MbO_2$ is not always an elementary reaction, and the overall rate constants, k_{on} and k_{off}, may be a composite of the rate constant for the bumpy path from solvent to binding site. Eyring *et al.* point out that reported O_2 affinities, obtained kinetically under the assumption of a single equilibrium step, only represent *apparent* equilibrium constants.[51]

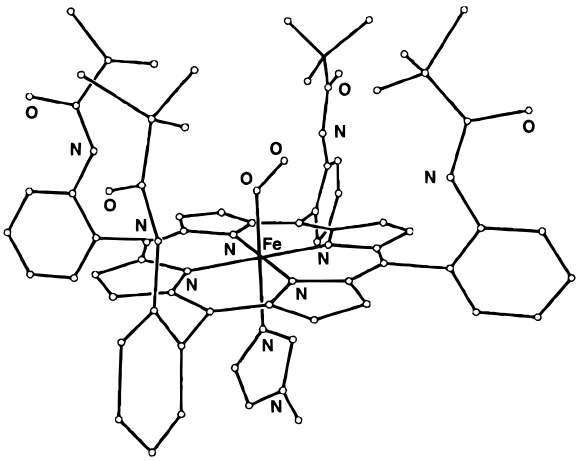

FIGURE 5. Crystal structure of dioxygen-bound picket fence porphyrin.

Synthetic Analogues of Hemoglobin and Myoglobin Proteins

Synthetic models of Hb and Mb have been invaluable in unraveling the subtle complexities of reversible O_2 binding and competitive inhibition by CO.[47,49,52−71] Model systems allow a systematic alteration which separately and collectively provides information on how Hb works. The subject of synthetic heme dioxygen binding has recently been reviewed.[48]

(1) Synthetic Models for Reversible Oxygenation. In principle, the necessary and sufficient conditions to mimic oxyHb in synthetic model systems are the formation of a 5-coordinate, high-spin heme precursor having a proximal base, as well as the prevention of μ-peroxo dimer formation.

The earliest structurally and functionally sound iron porphyrin model of the Hb and Mb active sites was the "picket fence" porphyrin.[72−75] This model binds O_2 reversibly, forming a diamagnetic O_2 complex as evidenced by its sharp ^{1}H NMR signals at room temperature. (A diamagnetic O_2 adduct is an important measure of reversible O_2 binding behavior of model complexes.) Dioxygen affinity studies of this model yielded values similar to those exhibited by Hb and Mb (Table 1). The crystal structure of the iron picket fence O_2 adduct was determined as shown in Figure 5.[76−78] Many O_2 binding porphyrin models were subsequently prepared and characterized.[64,76−81]

(2) The Competitive CO Binding Problem. The CO affinity of the picket fence porphyrin is more than 30 times that of Hb however.[82] If Hb or Mb had the same CO to O_2 affinity ratio (M value) as the picket fence porphyrin, mammals would suffocate from their own heme catabolism.

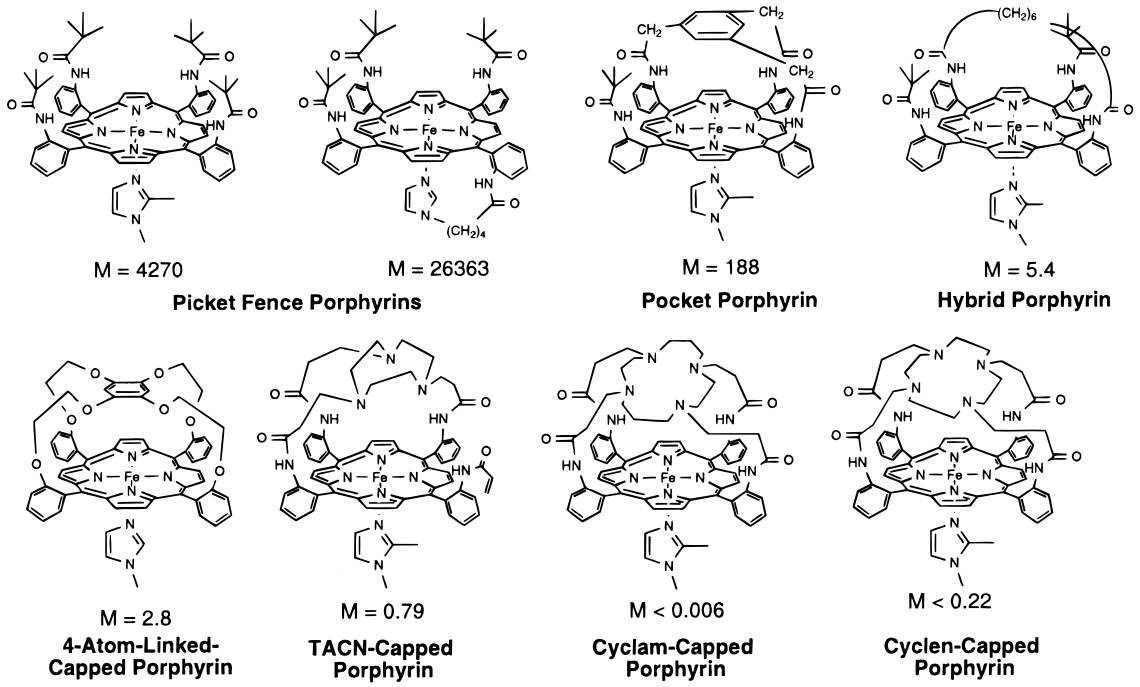

FIGURE 6. Dioxygen-binding myoglobin analogues.

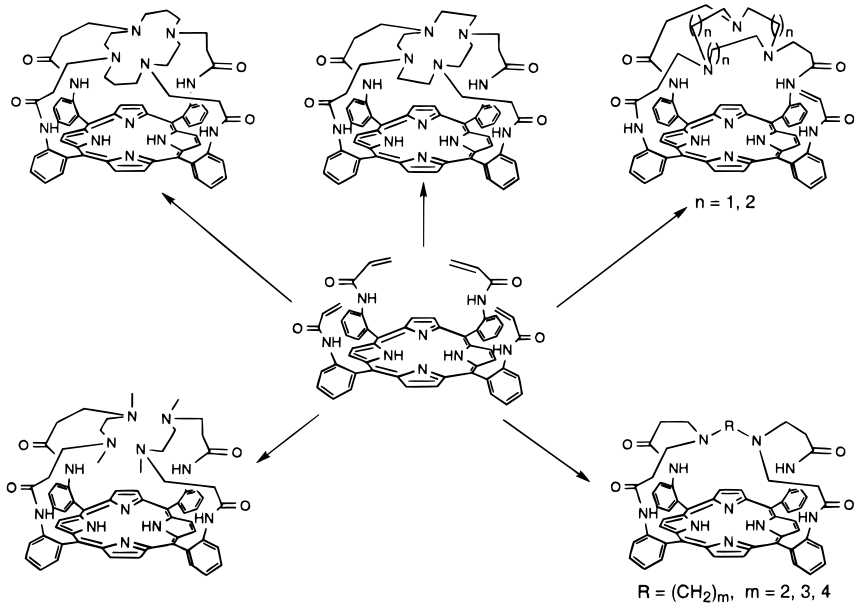

FIGURE 7. Capped porphyrins derived from the "congruent multiple Michael addition".

On the basis of picket fence models as well as Hb and Mb X-ray crystal structures, Collman *et al*. proposed that the distal histidine had a dual role of providing a H-bond to the coordinated O_2 and of decreasing CO affinity by sterically preventing CO from binding in a linear manner.[25,26] Dioxygen, binding in a bent fashion, should be free of such an interaction. Further work on the "pocket,"[82,83] "hybrid,"[84] and "capped"[68,85−90] porphyrins (Figure 6) has provided additional evidence (Table 1) for the plausibility of this hypothesis. For instance, the decreased size of the binding cavity in the pocket porphyrins resulted in *M* values on the order of 200. Infrared spectral studies of these compounds were consistent with a CO more weakly bound than in the case of picket fence porphyrin.[82,83] In addition to the steric effect, Traylor et al. demonstrate that the polarity of the gas binding packet has a large effect on the *M* value of model complexes. They argue that the *M* values in their studies are influenced by an increase in O_2 affinity with negligible change in CO affinity.[59,65]

(3) Our Recent Success. Recently we reported a versatile general method for attaching macrocycles over a porphyrin ring in a single high-yielding step.[91] This "congruent multiple Michael addition" (Figure 7) does not require high dilution and is facilitated by protic solvents and the presence of metals such as Fe(II), Co(II), and Zn(II) in the porphyrins. (More recently we reported two alternative synthetic methods[92,93] which greatly enhanced

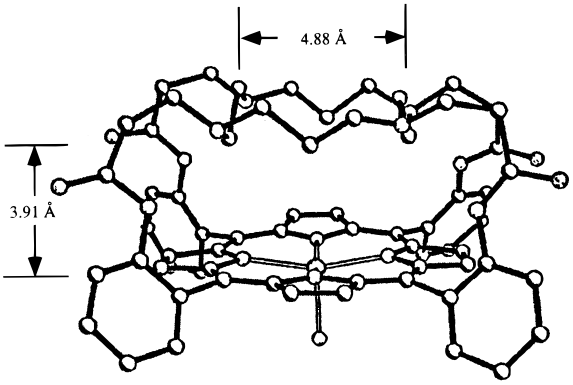

FIGURE 8. Crystal structure of cyclam-capped zinc porphyrin.

our ability to use them in conjuction with the Michael addition method: either to probe the effects of varying the length of the links between superstructure and porphyrin, or to add a nucleophile specifically to certain pickets and not to others by controlling the reaction conditions.) Using this new method, we designed, synthesized, and characterized a series of Mb active site analogues which differ in their gas binding cavity dimensions (see Figure 6), allowing us to reexamine steric effects on the equilibrium affinities of CO versus O_2.[94]

Carbon monoxide and dioxygen gas binding to these aza-crown-capped models was studied preliminarily by ^{1}H NMR spectroscopy in d_5-pyridine, which acts as both the solvent and the axial ligand. Whereas a paramagnetic NMR was observed with their O_2- and CO-free forms, indicating a 5-coordinate high-spin Fe(II) species, a diamagnetic NMR characteristic of a low-spin species was obtained upon O_2 and CO binding. (A more detailed discussion can be found elsewhere.[79,81,94−98]) Our quantitative gas titration data (Table 1) show that these aza-crown-capped models (Figure 6) manifest an even higher O_2 affinity but a much reduced CO affinity compared with Mb, resulting in *M* values close to 1.[94] The cyclam-capped porphyrin is particularly remarkable; while it exhibits a "normal" O_2 affinity, it does not bind CO at all (up to 1 atm of CO). The possible origin of this phenomenon can be understood by examining the crystal structure of the corresponding Zn(II) complex (Figure 8). The methylene groups from the aza cap have hydrogen atoms projected directly at an axis orthogonal to the porphyrin plane and directly above the metal porphyrin center. The intrinsically bent O_2 ligand would not suffer from a nonbonded interaction with these protons, but the CO ligand could be strongly distorted and therefore destabilized. This work again demonstrates that steric interactions can have profound effects on CO binding affinity; it also suggests that a steric effect cannot be ruled out as a major determinant of Hb's and Mb's CO affinities. Nonetheless, the detailed interaction between structural distortion and equilibrium affinities of CO remains controversial;[59,65,90,99−101] in our opinion the discrimination of CO is still a challenging question.

Stabilization of bound O_2 is also poorly understood. A distal histidine residue in Hb and Mb forms a weak H-bond to the terminal oxygen in the O_2 adduct. There have been several attempts to imitate such a H-bond with model Fe(II) porphyrins.[102−106]

In 1994, we reported a stable oxygen binding system involving iron and cobalt "picnic basket" porphyrins (Figure 9).[69] This family of porphyrins consists of a distal binding cavity with variable dimensions and an external bulky axial ligand on the proximal side. Our ^{1}H NMR and O_2 affinity measurements show that the iron and cobalt picnic basket porphyrins both bind O_2 reversibly at room temperature with high affinities. The O_2 affinity increases as the basket size decreases, indicating a dipole−dipole interaction between the terminally bound O_2 and the amide protons. The O_2 affinities of the cobalt picnic basket porphyrins are more sensitive to the change of basket sizes than those of the corresponding iron porphyrin, consistent with the proposal that Co−O_2 adducts have more electron density on the oxygen ligand than do the Fe−O_2 adducts.

Very recently, we introduced two generations of dendritic iron(II) porphyrins as synthetic models of globular hemoproteins in collaboration with scientists at ETH.[107] In analogy to the protein surroundings, the densely packed dendritic shell provides the iron heme with a hydrophobic environment which allows reversible oxygenation to be achieved.

The dendritic Fe(II) porphyrins were mixed with 1000 molar equivalents of 1,2-dimethylimidazole (1,2-Me_2Im), forming a 5-coordinate high-spin Fe(II) complex (Figure 10). (1,2-Me_2Im is known to form only a 1:1 high-spin adduct with Fe(II) porphyrins.[52]) The resulting Fe(II) porphyrin is therefore a good model for the lower affinity T-state of Hb.

Gas binding studies indicate that these dendritic Fe(II) porphyrins bind O_2 and CO reversibly. Quantitative gas

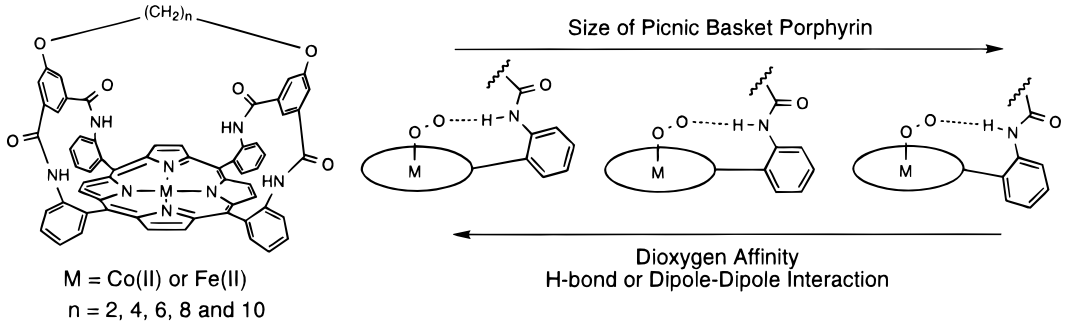

FIGURE 9. Picnic basket porphyrin.

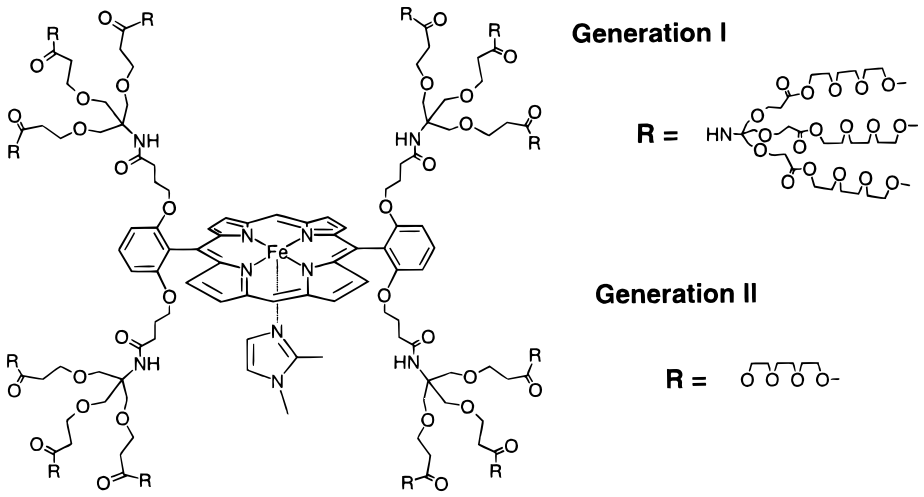

FIGURE 10. Dendritic iron(II) porphyrins.

titrations (Table 1) reveal that the CO affinities of the dendritic porphyrins are lower than those of the picket fence porphyrin but close to those of Hb, suggesting that, as with Hb, bound CO may experience an interaction that distorts binding from a favorable linear conformation.

Remarkably their O_2 affinities are about 1500 times greater than that of T-state hemoglobin, very close to those of the high-affinity Hb of the aforementioned bloodworm *Ascaris*. Why are the O_2 affinities so great? We propose that these may result from a H-bond between the amide group (see Figure 10) and the terminal coordinated oxygen atom. Our very recent EPR studies (unpublished results) on these Co(II)-substituted dendritic porphyrins provide strong evidence for this hypothesis of a H-bonding interaction.

Summary

Since the invention of the picket fence porphyrin, many attempts have been made to elucidate the factors responsible for gas binding specificity in hemoproteins. This account summarizes our contributions with model compounds. Emphasis is placed on our recent success in the design and synthesis of functional heme models. In this work, we present a class of aza-capped porphyrins that demonstrate the profound effects steric interactions can have on porphyrin CO affinity. With a series of iron and cobalt picnic basket porphyrins we have examined the dipole−dipole or H-bonding interaction between the terminally bound dioxygen and the amide protons. Comparison of their O_2 affinities indicates that electrostatic interactions between the amide groups of the picnic basket porphyrin and the CoO_2 species are more sensitive to the change of basket sizes than 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. We have also studied dendritic Fe(II) porphyrins as T-state Hb models. These dendritic porphyrins exhibit CO affinities similar to those of Hb but remarkably higher O_2 affinities, approaching that of Hb *Ascaris*. This striking result indicates that (1) as with Hb, bound CO experiences a destabilizing influence and (2) a H-bond between the terminal atom of bound O_2 and an amide group can drastically increases O_2 affinity. Our studies on heme models provide fundamental insights into the nature of O_2 adduct stabilization and CO ligand destabilization in hemoproteins.

Many issues remain unanswered, however. For instance, is the binding affinity affected predominantly by a single factor or by multiple factors? Does a steric effect that sharply reduces CO affinity actually require an observable geometric distortion? What are the spectroscopic signatures of this distortion? What is the role of kinetics *versus* thermodynamics? Resolution of these issues may provide further insights into ligand binding and discrimination in native hemoglobin and myoglobin.

We thank the NIH (Grant 5R37 GM-17880-26) and the NSF (Grant CHE9123187-A2) for financial support. We also thank Drs. John I. Brauman, Paul C. Herrmann, and Jean-Claude Marchon and Mr. Michael Eubanks for helpful discussions.

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AR9603064