JBIC (1997) 2:521–525

COMMENTARY

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Myoglobin models and steric origins of the discrimination between O_2 and CO

Received, accepted: 23 May 1997

Abstract Synthetic models of the myoglobin active site have provided much insight into factors that affect CO and O_2 binding in the proteins. "Capped" and "pocket" metal porphyrin systems have been developed to probe how steric factors affect ligand binding and ultimately to elucidate important aspects of the mechanism of CO discrimination in the proteins. These model porphyrins are among the most thoroughly characterized systems to date. From the twenty-one known crystal structures, analysis of the types of distortion that occur upon ligand binding under the cap, including porphyrin doming and ruffling, lateral and horizontal movement of the cap, and bending and tilting of the Fe–C–O bond, provides an indication of how steric interactions will affect structure in Hb and Mb. The model porphyrin systems discussed range from those that discriminate against O_2 binding compared to biological systems to those with similar CO and O_2 binding strength to myoglobin, and also to those that bind both O_2 and CO very weakly or not at all. The primary type of distortion observed upon CO binding is vertical or lateral movement of the cap and some ruffling of the porphyrin plane. Minimal bending or tilting of the M–C–O bond is observed, suggesting that the Fe–C–O bending that has been found from crystal structures of the hemoproteins is unlikely.

Key words X-ray structure · Biomimetic porphyrin · Iron · Ruthenium · Carbonyl

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Despite the fact that the oxygen-carrying hemoproteins hemoglobin (Hb) and myoglobin (Mb) are among the most studied of the proteins, the question of how structure affects CO and O_2 binding to their heme centers remains contentious. These proteins contain a square-planar heme [iron(II) protoporphyrin IX] that is embedded in the hydrophobic pocket of the globin; the heme and the globin are connected on the so-called proximal side by a covalent bond between the Fe center and a nitrogen atom of the imidazole group of a histidine residue. An open sixth coordination position on the distal side of the heme is the site of dioxygen binding. Other ligands, including CO, NO, and RNC bind at this site with respective affinities of approximately 10^2, 10^5, and 10^{-2} times those of O_2 [1]. The binding of CO has been of particular interest because it is discriminated against: although Hb and Mb bind CO more strongly than O_2, the M value [$M = P_{1/2}(O_2)/P_{1/2}(CO)$] for Hb and Mb is much smaller than it is for unprotected model porphyrin systems [2, 3]. This discrimination, which in energy terms amounts to about 4 kcal/mol, is vital, since CO is produced endogenously in various biological processes [2, 4], and approximately 3% of the heme sites in Hb are ligated by CO, even with the discrimination [5].

A central question that has led to intense study of biological [6] and model systems [5, 7] is how this discrimination occurs. Is O_2 binding stabilized or is CO binding destabilized in the biological systems? In fact, it is likely that both of these processes contribute to the lower value of M by very different chemical means. Electronic interactions, including hydrogen bonding between the bound oxygen molecule and the proton of a distal histidine [8], are believed to stabilize the more polar Fe–O_2 bond [6]. Steric interactions are believed to destabilize CO binding. The cavity in heme proteins has evolved to accommodate O_2 in its preferred bent geometry [9] but not CO in its preferred linear geometry [10]. As a result, for CO to bind at the iron center, distortion must occur through one or more energetically unfavorable processes, such as reorientation of the

globin, ruffling or doming of the porphyrin plane, tilting of the Fe–C–O axis, or bending of the Fe–C–O bond. Because O_2 is inherently bent, less distortion should be required to accommodate it. The structures of ligated Hb, Mb, and their mutants show considerable variability in porphyrin conformations and Fe–C–O and Fe–O–O angles [6, 11]. Nevertheless, crystallographic results [12–15] show significant bending or tilting or both of the Fe–C–O linkage, despite the linearity of such a linkage in unencumbered systems. However, the precision of such results, and hence meaningful correlations of perceived trends with binding constants, is limited by the low resolution of protein crystallographic studies [16, 17]. In fact, it is likely that errors in the Fe–C–O angle, when provided, are badly underestimated and could be as large as 25° [16]. Thus the importance of steric factors in the discrimination against the binding of CO remains unknown.

Because of the general complexity of the globin and its interaction with the heme, model systems, for which high resolution crystal structures can be obtained, have been developed to probe how steric factors affect ligand binding and ultimately to elucidate important aspects of the mechanism of CO discrimination. Through the attachment of diverse organic protecting groups to the distal face of model porphyrins, the size, shape, and functionality of such systems can be systematically varied so that steric and electronic factors for CO discrimination can be addressed individually. A large variety of model compounds have been prepared, including "chelated" [18, 19], "strapped" [20–26], "picnic basket" [27], "picket fence" [28, 29], "pocket" [30–32] and "capped" [33–40] porphyrins as well as hybrids [41–43] of these different classifications.

Here we comment on the model systems classified as "pocket" and "capped" porphyrins that specifically address steric effects on ligand binding. Related studies of strapped porphyrin systems are available [43]. The steric barrier in the pocket and capped porphyrins is created by tethering a 1,3,5-substituted or a 1,2,4,5-substituted benzene ring to the *ortho* positions of 5,10,15,20-tetraphenylporphyrin. The relevant capped and pocket porphyrins are sketched in Fig. 1. With these systems, the degree of steric protection incorporated into the porphyrin is generally defined by the number of linkage atoms in the arms. For example, $H_2(OC_2OPor)$, with an –O–CH_2–CH_2–O– linkage, is referred to as a four-atom-linked capped porphyrin.

Pocket and capped porphyrins have been extensively characterized by single-crystal X-ray diffraction methods. Although it is difficult to make direct comparisons of CO and O_2 binding constants for different systems because of the variety of conditions used in obtaining such data [7, 44], comparisons of general trends in binding constants with the structural changes that result from steric interactions upon ligation are useful in predicting the modes of steric discrimination in the ligation of Hb and Mb. It is convenient to discuss the trends in CO and O_2 binding in terms of two types of distal steric interactions defined in model systems: central (from directly above) and peripheral (from the sides) [45]. Central steric interactions should have a strong effect on the linear binding of CO, whereas peripheral steric interactions should have little or no effect on CO binding but a strong effect on O_2 binding. As the steric barrier becomes significant, types of distortions predicted in both proteins and model compounds include: (1) increased porphyrin ruffling or doming, (2) greater expansion of the distal protective group and, if there are central effects on CO binding, (3) tilting or bending of the Fe–C–O linkage or both.

These capped and pocket porphyrin Fe(II) model systems of Fig. 1 can be divided into four categories on the basis of their values of $P_{1/2}(O_2)$, $P_{1/2}(CO)$, and M: (1) porphyrins for which no conclusions can be drawn regarding steric effects on ligand binding, (2) porphyrins that discriminate against O_2 binding since they bind O_2 with less affinity but CO with about the same affinity as Hb and Mb, (3) porphyrins that show discrimination similar to Hb and Mb, and (4) porphyrins for which O_2 and CO affinities are significantly lower than in Hb and Mb. We proceed to provide examples from these four categories.

The C_4-Cap system is an example of Category 1. Structural characterization of this system makes it clear

Fig. 1 Connectivity of capped and pocket porphyrins

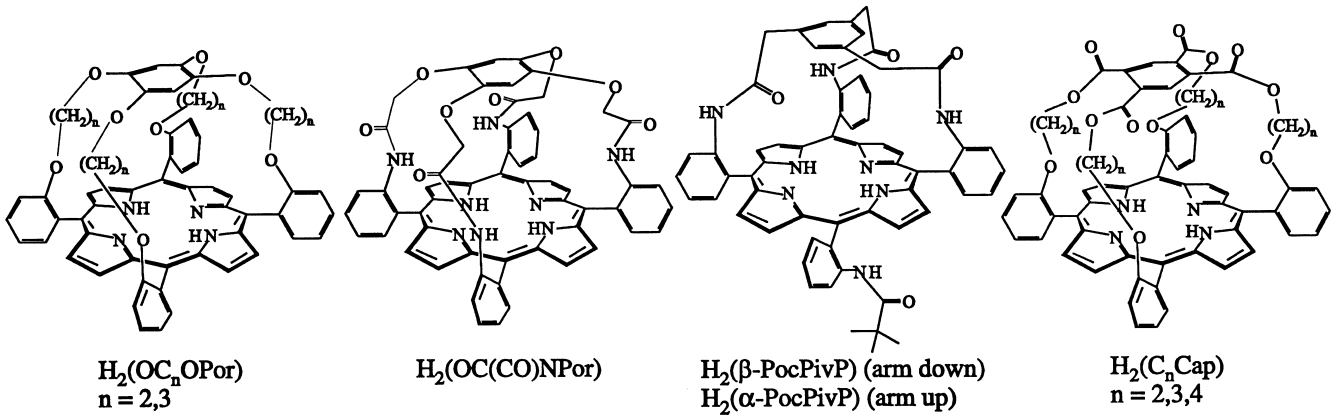

Table 1 O_2 and CO binding to Fe^{II} porphyrin complexes and hemoproteins[a]

	$P_{1/2}(O_2)$(Torr)	$P_{1/2}$(CO)(Torr)	$M = P_{1/2}(O_2)/P_{1/2}$(CO)	Reference
Mb (elephant)[b]	0.62	9.5×10^{-2}	6.5	56
Mb (horse)[b]	0.70	1.8×10^{-2}	39	1
R-state systems				
HbA(R)[b]	0.22(α)[d], 0.36(β)[d]	1.4×10^{-3} [d]	160(α), 260(β)	30, 57–60
Fe(PocPivP)(1-MeIm)	0.36	1.5×10^{-3}	240	30
Fe(OC_2OPor)(1-MeIm)	61[f]	100, 40[c], 17[g]	–	54
Fe(OC(CO)NPor)	$>7.7\times10^{4}$	$>7.7\times10^{4}$	–	54
Fe(C_2-Cap)(1-MeIm)	23, 4.5[c]	5.4×10^{-3}	4300	61, 62
Fe(C_2-Cap)(1,5-DCIm)	–	7.5×10^{-3}	–	35
Fe(C_3-Cap)(1,5-DCIm)	54[c]	4.1×10^{-3}	–	62
Fe(C_4-Cap)(1,5-DCIm)	–	0.21	–	35
T-state systems				
HbA(T)[b]	40(α)[d], 140(β)[d]	0.3[d]	130(α), 470(α)	30, 59, 60, 63
Fe(PocPivP)(1,2-Me_2Im)	12.6	6.7×10^{-2}	220	30
Fe(OC_2OPor)(1,2-Me_2Im)	>760	~5000	–	54
Fe(C_2-Cap)(1,2-Me_2Im)	4000	0.2	2.0×10^{4}	61, 62
Fe(C_3-Cap)(1,2-Me_2Im)	880[e]	0.14		64
Fe(C_4-Cap)(1,2-Me_2Im)	–	4.1	–	35

[a] Measurements were made in toluene at 25 °C unless otherwise noted
[b] H_2O, pH ~7
[c] 0 °C
[d] 20 °C
[e] −63 °C
[f] −43 °C
[g] −20 °C

that solvents get trapped under the cap [46]. This seven-atom-linked capped porphyrin system is conceivably of use as a model for solvent displacement, such as a water in hemoglobin, but it is not of use as a probe of steric effects.

The C_3-Cap, C_2-Cap, and OC_3OPor systems are examples of Category 2 (models that discriminate against O_2 binding). In these systems, the $P_{1/2}$(CO) value is within an order of magnitude of that reported for Hb, whereas the $P_{1/2}(O_2)$ value is approximately two orders of magnitude greater than for Hb (Table 1). Presumably, peripheral steric effects are stronger here than in the proteins, but the central steric effects are about the same [47]. The four five-atom or six-atom linkages connecting the benzene cap to the porphyrin can readily expand vertically to accommodate a linear CO ligand, but such arms severely impair horizontal movement of the cap. Additional energy is required to accomplish such movement, which is needed to accommodate the bent Fe–O–O linkage, and a higher value of $P_{1/2}(O_2)$ results. Comparison of the structure of the free base, H_2(C_3-Cap), with that of the carbonyl, Fe(C_3-Cap)(CO)(1-MeIm), indicates that the vertical flexibility is available: the cap expands 2.3 Å, from ~3.5 Å to ~5.9 Å, upon CO ligation [46]. Similarly, C_2-Cap expands ~1.6 Å and OC_3OPor expands ~0.9 Å, to ~5.6 Å, upon CO ligation (Table 2) [47–49]. In all three systems, lateral movement of the cap and distortion of the porphyrin plane are minimal, and the Fe–C–O bond remain essentially linear and untilted.

The PocPivP system, for which the O_2 and CO affinities are close to those for Hb and Mb (Table 1), is an example of Category 3. From a comparison of the structure of H_2(α-PocPivP) [46] with those of Ru(β-PocPivP)$(H_2O)_{in}(CO)_{out}$ [50], Ru(α-PocPivP)(CO)(1-MeIm) [51], and Fe(β-PocPivP)(CO)(1,2-Me_2Im) [52], it is apparent that horizontal displacement of the cap is the main type of distortion that occurs when CO or H_2O binds under the cap (Table 2). The cap moves laterally as much as 1.44 Å, from 1.86 Å in H_2(α-PocPivP) to 3.30 Å in Fe(β-PocPivP)(CO)(1,2-Me_2Im). The three-atom arms of the pocket porphyrin severely limit vertical expansion of the cap, but the lack of a fourth arm allows the cap to move sideways to minimize steric interactions. Steric strain may also cause increased distortion of the porphyrin plane, but this also appears to be a function of whether the pivalamido arm is oriented up (α) or down (β) and may simply be a manifestation of crystal packing effects.

The four-atom-linked porphyrins OC_2OPor and OC(CO)NPor [38, 53], the most sterically encumbered porphyrins reported to date, are examples of Category 4 (systems that show CO and O_2 affinities significantly lower than do Hb and Mb). O_2 and CO binding studies with these capped porphyrins indicate that steric factors *do* affect CO binding: the OC_2OPor system has one of the highest $P_{1/2}$(CO) values, 100 Torr at 25 °C [54] measured to date for any system, biological or model, although there is one example of a system that does not bind CO at 760 Torr [40], and OC(CO)NPor does not bind CO or O_2 even at a pressure of 7.6×10^{4} Torr [54]. Because these values of $P_{1/2}$(CO) are so much higher than those for Hb and Mb, we conclude that steric effects on ligation of Hb and Mb are small compared with such effects in these models. Therefore, if CO does not bend or tilt in the OC_2OPor

Table 2 Porphyrin distortions

Structure	Average deviation from 24-atom plane (Å)	Vertical displacement of cap (Å)[a]	Lateral displacement of cap (Å)[b]	<M−C−O	Reference
H_2(α-PocPivP)	0.10	4.21	1.86	–	46
Ru(β-PocPivP)(H_2O)$_{in}$(CO)$_{out}$	0.21	4.23	3.01	178.7(3)	50
Ru(α-PocPivP)(CO)(1-MeIm)	0.13	4.39	2.82	168(3)	51
	0.15	4.37	2.74	159(3)	
Fe(β-PocPivP)(CO)(1,2-Me_2Im)	0.27	4.25	3.30	172.5(6)	52
H_2(OC_2OPor)	0.10	3.81	0.54	–	38
[Fe(OC_2OPor)]$_2$(μ-O)	0.05	3.46	0	–	53
Fe(OC_2OPor)(OMe)	0.07	3.93	0.54	–	53
Ru(OC_2OPor)(H_2O)$_{in}$(CO)$_{out}$	0.06	4.80	0.60	178.1(4)	50
H_2[OC(CO)NPor]	0.06	3.90	1.10	–	38
H_2OC_3OPor)	0.07	4.74	0.54	–	49
Fe(OC_3OPor)(CI)	0.15	4.65	1.35	–	49
Fe(OC_3OPor)(CO)(1-MeIm)	0.08	5.55	0.21	173.9(7)	49
Fe(OC_3OPor)(CO)(1,2-Me_2Im)	0.07	5.59	0.66	180.0[c]	49
H_2(C_2-Cap)	0.13	3.96	0.12	–	48
Fe(C_2-Cap)(Cl)	0.08	4.01	0.24	–	65
Fe(C_2-Cap)(CO)(1-MeIm)	0.08	5.57	0.30	172.9(6)	47
	0.08	5.67	0.00	175.9(6)	
H_2(C_3-Cap)	0.27	3.49	0.20	–	46
Co(C_3-Cap)	0.31	3.50	0.20	–	66
Fe(C_3-Cap)(CO)(1-MeIm)	0.04	5.86	1.03	178.0(13)	46
H_2(C_4-Cap)	0.08	7.28	0.69	–	46
Fe(C_4-Cap)(Cl)	0.04	7.12	0.40	–	46
	0.07	7.66	0.52	–	

[a] The vertical displacement of the cap is the perpendicular distance of the cap centroid from the mean 24-atom porphyrin plane

[b] The lateral displacement of the cap is defined as the distance of the cap centroid from the above perpendicular

[c] By symmetry

system, it probably is not bent in Hb or Mb. What is the structural basis for the steric discrimination against CO binding in these four-atom-linked capped porphyrins? Unfortunately, the structure of Fe(OC_2OPor)(CO)(base) is not known. In the structure of Ru(OC_2OPor)(H_2O)$_{in}$(CO)$_{out}$ [50], the cap centroid lies 4.8 Å above the porphyrin plane. From the three carbonyl structures reported for five-atom-linked capped porphyrin systems, which all have a cap-to-porphyrin distance of ~5.6 Å, it appears that the cap in OC_2OPor must expand an additional 0.8 Å to accommodate a linear Fe–C–O linkage. Preliminary EXAFS results [H.C. Freeman, D. Shi, P.J. Ellis, B. Hedman, K.O. Hodgson, C. Slebodnick, J.A. Ibers, unpublished results] on Fe(OC_2OPor)(CO)(1-MeIm) are consistent with a linear Fe–C–O linkage. Hence structural reorientation must occur through distortion of the cap and porphyrin. To bind CO or O_2 to Fe(OC(CO)NPor) would require vertical expansion of the cap with concomitant non-planarity of the amide groups in each arm. This process is so energetically unfavorable as to preclude such binding, even at very high pressures.

In summary, with the exception of one structure [Ru(α-PocPivP)(CO)(1-MeIm)] of relatively poor quality, where the two independent Ru–C–O angles are 159(3)° and 168(3)° (Table 2) [51], structural data for the other systems discussed here show ruffling of the porphyrin ring and lateral or vertical movements of the benzene cap, but no M–C–O angles < 172° (M = Fe or Ru), despite the intense steric constraints engendered by some of these systems. It therefore seems unlikely to us that the Fe–C–O bending reported in Mb to be a major form of distortion upon CO ligation is real. The precision with which Fe–C–O angles are known in these protein structures has been greatly overestimated [16, 17], and so the entire issue of significantly non-linear Fe–C–O bonds in hemoproteins may be moot. Although a recent calculation [55] suggests that the energy required to distort the Fe–C–O linkage is small, the structural results discussed here suggest that in the model systems steric effects are manifested in distortions of the porphyrin core rather than in the Fe–C–O linkage. Unfortunately, the precision of structure determinations of the proteins precludes an analysis of the fine details of porphyrin ruffling or doming, where it thus appears more likely that steric effects will be seen. Whether such steric effects play a significant role in the destabilization of CO binding or whether discrimination results primarily from stabilization of O_2 binding through hydrogen bonding remains an open question.

Acknowledgment This research was supported by the US National Institutes of Health [Grant HL13157 (J.A.I.)].

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