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On Carbon Monoxide and Dioxygen Binding by Iron(II) Porphyrinato Systems

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On Carbon Monoxide and Dioxygen Binding by Iron(II) Porphyrinato Systems

The current literature on the binding of dioxygen and carbon monoxide to iron(II) porphyrinato systems is reviewed. Conditions of measurement and their errors are considered in arriving at a selection of systems that are believed to be comparable. The data from these systems are tabulated and are used to enumerate some of the factors that influence ligand binding.

INTRODUCTION

That the general ligand binding properties and structures of iron(II) and cobalt(II) porphyrinato model complexes have provided many insights into structure-function relationships of dioxygen-binding hemoproteins is scarcely disputable.[1-10] For example, the stereochemistries of various iron porphyrinato systems and their adducts with nitrogenous bases[6,7] and ligands such as dioxygen,[7,8] carbon monoxide,[6,9] and nitric oxide[10] have been defined with a precision and accuracy much greater than is currently obtainable with protein crystal structures. They have provided benchmarks against which the reasonableness of the protein structures can be assessed.[5] In these structures dioxygen has been found to adopt an end-on bent geometry **I**,[7,8] whereas carbon monoxide has been found generally to adopt a linear geometry **II**,[9] a geometry that in many hemoglobins may be impeded by distal groups hovering over the iron center[1,11]:

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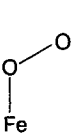
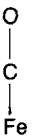


I

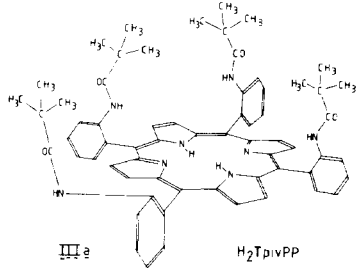


II

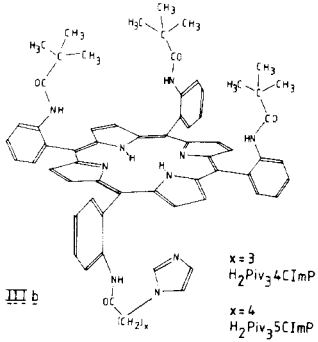
These structures, and those of related cobalt systems,[12] have clarified concepts of the cooperative ligand binding by hemoglobin.[1,6,13–15] Further, conditions necessary for the reversible binding of dioxygen and the isolation of moderately stable iron dioxygen species at *ambient* temperatures have been established—a protected binding site for dioxygen that hinders bimolecular $FeO_2 \cdots Fe$ contact and a relatively aprotic environment.[3,16–19] Dioxygen binding may be examined at low temperatures by the usual spectroscopic methods, where not only is such binding stronger but reactions that lead to irreversible oxidation are disfavored,[20–25] and at ambient temperatures by rapid kinetic methods.[26–33]

These are, however, mostly broad features. That the current *detailed* thermodynamic and kinetic studies on ligand binding by available model complexes[3,4,26–44]contribute directly to increased understanding of ligand binding by the hemoglobins is rather less certain. Many seemingly anomalous results from these model systems have now accumulated. For example, some of the iron picket-fence porphyrins derived from **IIIa** have an enormously high carbon monoxide affinity compared with the apparently less hindered iron derivatives of the flat-open porphyrins, **IV.** (See Table I[28,34,35,39,40,43,45–48] for a detailed collation of values that will be examined in more detail later.) For iron derivatives of the cap system, **Va,** substitution of 1-MeIm by 1,2-Me_2Im reduces O_2 affinity by a factor of 200 whereas for a picket-fence derivative Fe(PocPiv) derived from **IIIc,** a reduction of less than 40 occurs. The iron derivatives of the flat-open porphyrin system bind CO with approximately the same affinity as those of the apparently sterically congested caps. The O_2 affinity of the iron derivatives of the flat-open porphyrins, **IV,** is orders of magnitude less than that for hemoglobin *Ascaris* while conversely CO affinity is orders of magnitude greater (see Tables I and II[49–61]).

Latent anthropomorphism is responsible, in part, for the concentration



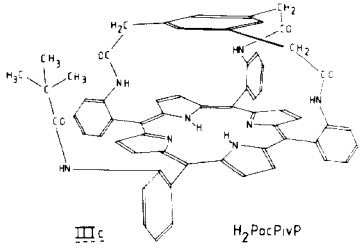
III a H_2TpivPP



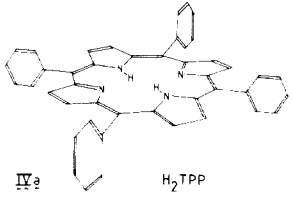
III b

x = 3
$H_2Piv_34ClImP$

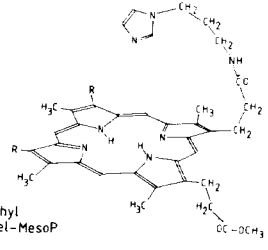
x = 4
$H_2Piv_35ClImP$



III c H_2PacPivP



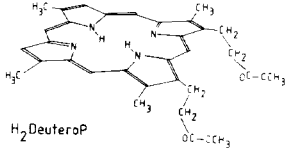
IV a H_2TPP



R = Ethyl
H_2Chel-MesoP

R = Vinyl
H_2Chel-ProtoP

IV b



H_2DeuteroP

IV c

TABLE I Selected values of $P_{1/2}$ (in Torr) for CO and O_2 binding to iron(II)

Compound	T(°C)	Solvent
Flat-open		
1 Fe(TPP)(1,2-Me_2Im)	25	toluene
2 Fe(T(o-OMeP)P)(1,2-Me_2Im)	25	toluene
3 Fe(Chel-ProtoP)	20	benzene
4 Fe(Chel-MesoP)	20	90:10 tol/CH_2Cl_2
Picket		
11 Fe(TpivPP)(1,2-Me_2Im)	25	toluene
12 Fe($Piv_3$5ClmP)	25	toluene
13 Fe(PocPiv)(1-MeIm)	25	toluene
14 Fe(PocPiv)(1,2-Me_2Im)	25	toluene
Strap		
21 Fe(7,7-cyclophane)-(1,5-Cy_2Im)	20	benzene
22 Fe(6,6-cyclopane)-(1,5-Cy_2Im)	20	benzene
23 Fe(SP-13)(1-MeIm)	20–22	benzene
24 Fe(SP-14)(1,5-Cy_2Im)	20–22	benzene
25 Fe(SP-15)(1,5-Cy_2Im)	20–22	benzene
Cap		
31 Fe(C_2Cap)(1-MeIm)	25 0	toluene
32 Fe(C_2Cap)(1,2-Me_2Im)	25 0	toluene
33 Fe(C_3Cap)(1,5-Cy_2Im)	25 0	toluene
34 Fe(C_3Cap)(1,2-Me_2Im)	25 0	toluene
35 Fe(NapC_2Cap)(1-MeIm)	25 0	toluene
36 Fe(NapC_2Cap)(1,2-Me_2Im)	25 0	toluene
37 Fe(C_2Cap-NO_2)(1-MeIm)	25 0	toluene
38 Fe(C_2Cap-NO_2)(1,2-Me_2Im)	25 0	toluene
Diporphyrin		
41 FeCu(4-diporphyrin)(1-MeIm)	20–22	benzene
42 FeCu(4-diporphyrin)(THPIm)	20–22	benzene
43 FeCu(5-diporphyrin)(THPIm)	20–22	benzene

porphyrinato imidazole systems[a] (see overleaf for footnotes)

$P_{1/2}^{O_2}$	$P_{1/2}^{CO}$	$M = P_{1/2}^{O_2}/P_{1/2}^{CO}$	Base mol/l	Reference
...	1.4×10^{-1}	...	3.1×10^{-3}	b
...	8.0×10^{-2}	...	3.1×10^{-3}	b
5.6	2.5×10^{-4}	2.2×10^{4}	...	c
2.8	5.0×10^{-4}	5.6×10^{3}	...	c
38	8.9×10^{-3}	4.3×10^{3}	~0.01	d
0.58	2.2×10^{-5}	2.7×10^{4}	...	d
0.36	1.5×10^{-3}	2.7×10^{2}	0.1–1.0	e
12.6	6.7×10^{-2}	2.2×10^{2}	0.1–1.0	e
1.4	9.1×10^{-4}	1.5×10^{3}	0.03–0.08	f
7.0×10^{2}	1.7×10^{-1}	4.1×10^{3}	1.2	f
...	1.2×10^{1}		0.2	g
...	5×10^{-1}		1.0	g
15	5×10^{-2}	3.0×10^{2}	0.2	g
23	5.4×10^{-3}	4.3×10^{3}	1.0	h
4.5	7.6×10^{-4}	5.9×10^{3}		
4.0×10^{3}	2.0×10^{-1}	2.0×10^{4}	1.0	h
9.3×10^{2}	1.7×10^{-2}	5.5×10^{4}		
...	4.1×10^{-3}		0.1 (O_2)	i
5.4×10^{1}	...		1.0 (CO)	
...	1.4×10^{-1}		0.1	i
...	3.0×10^{-2}			
...	2.9×10^{-3}		1.0	i
2.3				
...	1.0×10^{-1}		1.0	i
6.1×10^{2}	...			
...	7.0×10^{-3}		1.0	i
7.1				
...	5.1×10^{-1}		1.0	i
...				
31	1.0×10^{-1}	3.1×10^{2}	0.2	g
...	1.3×10^{-1}	...	1.0	g
5	2.0×10^{-2}	2.5×10^{2}	0.2	g

TABLE I *(continued)*

[a]Here and elsewhere the following conversion factors are used to reduce equilibrium constants expressed as $K(M^{-1})$ into $P_{1/2}$ in Torr. For DMF/H_2O systems a linear interpolation was made based on solubilities for O_2 in DMF and H_2O. For 90:10 toluene/CH_2Cl_2 systems, the solubility of O_2 or CO in toluene was assumed. For the solubility of O_2 or CO in CH_2Cl_2 the value was taken by analogy with those for $CHCl_3$ and CCl_4. Insofar as it was possible to locate them we have endeavored to use the solubilities used by Traylor and co-workers. Solubilities for O_2 in DMF and toluene of 7.4 to 10^{-6} M/Torr and 1.17 10^{-5} M/Torr have been measured.[45] Errors in converting K back to $P_{1/2}$ should be less than 20%.

Solvent	O_2 (M/Torr)	CO(M/Torr)
benzene[46]	1.2×10^{-5}	9.97×10^{-6}
toluene[48]	1.02×10^{-5}	1.02×10^{-5}
DMF[48]	5.9×10^{-6}	3.5×10^{-6}
CH_2Cl_2 [48]	1.17×10^{-5}	1.17×10^{-6}
H_2O [47]	1.82×10^{-6}	1.36×10^{-6}

[b]Reference 35.

[c]Reference 28. Values reported as $K(M^{-1})$ obtained from the ratio of kinetic constants k_{on}/k_{off}. For k_{off}^{CO} values the reader is referred (in Ref. 28) to Ref. 32, where the k_{off} value for Fe(chel-ProtoP) is determined in 95:05 toluene/methanol and that for Fe(chel-MesoP) in 80:20 methanol/water. $K(M^{-1})$ values are converted to $P_{1/2}$ values using the solubilities supplied in Ref. 28: 1.2 10^{-5}M/Torr for O_2 and 9.97 10^{-5}M/Torr for CO in benzene.

[d]Reference 40 for $P_{1/2}^{O_2}$ (estimated error ±5%); reference 38 for $P_{1/2}^{CO}$ (estimated errors ±10%).

[e]Reference 39. Value for M determined experimentally. Estimated error 15%.

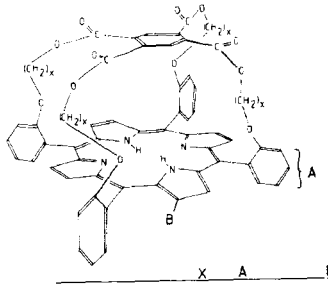
[f]Reference 28. Estimated error in rate constants ±10% for the 7,7-cyclophane species and ±20% for the 6,6-cyclophane.

[g]Reference 43. Errors ±20% between $P_{1/2}$ measured kinetically and thermodynamically.

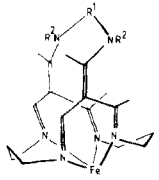
[h]Reference 34. Values for $P_{1/2}^{O_2}$ at 25°C calculated from ΔH and $T\Delta S$ contributions. Values for $P_{1/2}^{CO}$ from Ref. 35. Estimated errors ±10%.

[i]Reference 35. Estimated errors ±5% for $P_{1/2}^{O_2}$ and ±10% for $P_{1/2}^{CO}$.

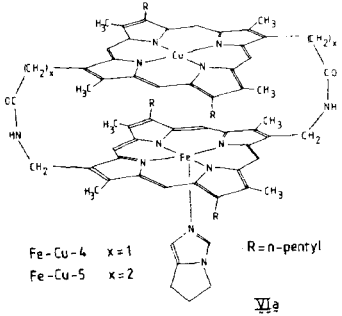
on mammalian or vertebrate hemoglobins whose properties represent optimal adaptation to an external environment where the partial pressure of dioxygen is about 250 Torr. Dioxygen binding to myoglobin (Mb) and hemoglobin (Hb) in the R (relaxed) conformation has often been implicitly considered as representative of binding in a sterically unconstrained environment, whereas carbon monoxide binding may be strongly discouraged by the distal histidine residue.[1,3,37] However, the recent structure determination of oxymyoglobin shows on the one hand that the dioxygen ligand adopts a sterically unfavorable eclipsing conformation with respect to an Fe-N(porphyrinato) bond, and on the other hand that it is hydrogen bonded to the distal histidine residue.[62,63] For the model compounds Fe(TpivPP)(1-MeIm)(O_2)[8] and Fe(TpivPP)(2-



		X	A	B
Va	H_2C_2Cap	2	phenyl	H
Vb	H_2C_3Cap	3	phenyl	H
Vc	H_2NapC_2Cap	2	naphthyl	H
Vd	$H_2C_2CapNO_2$	2	phenyl	NO_2



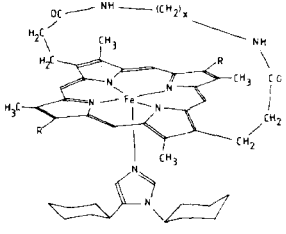
VII lacunar species



Fe-Cu-4 x = 1
Fe-Cu-5 x = 2

R = n-pentyl

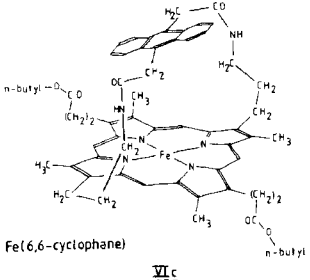
VIa



Fe(SP-13) x = 5
Fe(SP-14) x = 6
Fe(SP-15) x = 7

R = n-pentyl

VIb



Fe(6,6-cyclophane)

VIc

TABLE II
Dioxygen and carbon monoxide affinities (in Torr) of selected hemoglobins

Hemoglobin	Reference	$P_{1/2}^{O_2}$	$P_{1/2}^{CO}$ (°C)	M
Hb *Ascaris*	49	$1–4 \times 10^{-3}$	1×10^{-1} (20)	≈0.036
	50[a]	4.7×10^{-3}	6.3×10^{-2} (27.5)	0.075
legHb	51[b]	4.7×10^{-2}	7.4×10^{-4} (20)	64
	51[c]	4.5×10^{-2}	7.1×10^{-4} (25)	63
HorseMb	54	7.0×10^{-1}	1.8×10^{-2} (20)	39
Hb *Aphrodite*	55[d]	1.1	6.5×10^{-3} (20)	167
Hb^{A}R	38[e]	0.15–1.5	$1–4 \times 10^{-3}$	200–250
Hb^{A}T	38[e]	9–160	$1–2.8 \times 10^{-1}$	32–1600

[a]These values are obtained from the ratios for the rate of binding and of dissociation, k_{on}/k_{off}, and converted using the following values for the solubility of O_2 and CO in water; 1.82×10^{-6} M/Torr and 1.36×10^{-6} M/Torr.[47]

[b]The value for $P_{1/2}^{O_2}$ was calculated from $P_{1/2}^{CO}$ and M. Appleby reported a value of 4×10^{-2} Torr from direct measurements (Ref. 52).

[c]Values obtained from the ratio k_{on}/k_{off}. An independent value for $k_{on}^{O_2}/k_{off}^{O_2}$ of 2.1×10^{-2} Torr [20°C] has been obtained (Ref. 53). See footnote b for conversion. [d]$P_{1/2}^{CO}$ is calculated from $P_{1/2}^{O_2}/M$.

[e]The values reported therein were derived from the data of others [Ref. 54, 56–61); they are sensitive to pH, ionic strength, phosphate concentration, etc.

MeIm)(O_2)[7] the dioxygen ligand adopts a bisecting conformation with respect to Fe-N(porphyrinato) bonds but it is not hydrogen bonded to any distal moiety. Thus the remarkable similarity in O_2 affinity, recorded as $P_{1/2}$, between Fe(TpivPP)(1-MeIm) and R-state Hb and Mb must be a fortuitous compensation of competing effects.

In some instances we may know more about the protein than the model. For example, there is evidence that ligand binding to Mb at low temperatures is a four-step process,[64] whereas that to isolated protoheme may be a two-step process.[65] The mechanism of binding in the model micellized hemes is currently unknown.[4,26,29–33] It is interesting that the overall rate constants for ligand binding to micellized heme systems and to Hb, but not Mb, are very similar. The influence of the micelle on the stereochemistry of the heme and the degree of encapsulation of the heme into the micelle are less characterized than the analogous structural parameters for many hemoglobins.

There is an enormous range in the dioxygen affinities of hemoglobins (Table II) that is not paralleled by current model systems (Table I).

While there exists a 10^2 difference in O_2 affinity between the R and T states of Hb there also exist invertebrate hemoglobins with affinities 10^3 greater than R state Hb (for example, $P_{1/2}^{O_2} = 0.0015$ Torr at 20°C for Hb *Ascaris*[50]). We have discussed in a general way possible factors that may promote ligand affinity[5] but we still know remarkably little about the specific influences exerted by the protein. Our understanding of structure–function relationships in the more studied vertebrate hemoglobin systems would increase significantly if we knew more about the very high-affinity oxygen-binding hemoproteins. Models for such systems would be very useful, but none exists at this time. Rather we must be satisfied at present with the substantial mass of detailed kinetic and thermodynamic data on model systems for the vertebrate hemoproteins that reflect the rapid advances in experimental techniques since the early largely qualitative reports of 1973–1974. A comprehensive review is therefore timely. Although the utility of these systems as *quantitative* models for ligand binding by the hemoproteins is dubious, an understanding of the trends in ligand binding and their possible origins in these models is undoubtedly of considerable importance in the *qualitative* assessment of structure–function relationships in the hemoproteins. Moreover, interpretation of results from the model systems poses in itself a fascinating problem in inorganic chemistry.

ERRORS IN MEASUREMENT AND COMPARISON OF DATA

Before we proceed further, a discussion of errors and what may be validly compared (similar to that undertaken in assessing precision and accuracy of protein crystal structures with respect to model compounds[5]) seems warranted.

Reproducibility and Accuracy

The groups of Basolo and Baldwin, Chang, Collman and Traylor, whose data on Fe systems comprise the bulk of Table I, have on occasions provided estimates on the precision or reproducibility of their equilibrium and kinetic data. A value of $\pm 10\%$ is often provided, although lower and higher estimates can be found, the latter where competing equilibria, incomplete saturation or instability occur. As documented in Table II and its footnotes, the agreement is good between ligand affinities of hemoglobins measured kinetically and thermodynamically. Such reassurance is not yet forthcoming for the various systems tabulated in

Table I, with a few exceptions.[44,66] *In general, precision to within 15% may be possible; accuracy to better than 50% has yet to be demonstrated.* These errors are certainly frustratingly large in magnitude but they are intrinsic to the complexity of the systems being studied.

Given these error estimates for a given datum, at what level can differences among data be considered significant and interpretable? It is often possible in a given experiment to observe small (~ twofold) but significant changes of ligand affinity as a function of a single variable, e.g., temperature. In systems where two experiments must be carried out to obtain a comparison, e.g., the effects of changing an axial base, we believe that fivefold changes in affinity may not only be significant but also interpretable. A difference in affinity of ~10 corresponds to a free-energy difference of only ~1.5 kcal/mol at 25°C. The comparisons to be made are not always among systems that are strictly comparable (see below). Accordingly, we take the view that differences of at least a factor of 10 in K or $P_{1/2}$ values should obtain before perceived differences can be justified. And when comparison of the values of the partition coefficient $M = P_{1/2}^{O_2}/P_{1/2}^{CO}$ is made, a factor of at least 20 is necessary before we consider the difference significant. Note that our criteria for significance are generally much more conservative than are those in the literature.

Comparability of Systems

Unfortunately, the many systems among which comparisons would be interesting are often not comparable with respect to (1) temperature, (2) axial base concentration, (3) solvent polarity, (4) porphyrin and (5) axial base. Let us now examine these effects (Table III[28–31,35,38,40,44,45,67,68]). First, as a result of different enthalpy and entropy contributions to the free energy for the coordination of CO to Fe(C_2Cap)(1,2-Me_2Im), **32**, and Fe(C_3Cap)(1,2-Me_2Im), **34**, the $P_{1/2}$ values show a reversal in ordering with change in temperature that appears to be significant. The affinities for CO and O_2 of the chelated protoheme species, **3**, in a 2% aqueous MTAB suspension both vary by more than a factor of 5 for a temperature change of 20° (15–35°C).[29] There may be a differential temperature effect on the binding of CO and O_2: the partition coefficient M appears to increase with decreasing temperature although the effect is less than fivefold for a change in temperature of 25°C (see Table I). We note parenthetically that partition

TABLE III
Effects of temperature, solvent and porphyrin substituents on ligand affinities[a]

	$P_{1/2}^{CO}$ (°C)	$P_{1/2}^{CO}$ (°C)
Temperature		
32 Fe(C_2Cap)(1,2-Me_2Im)[b]	2.0×10^{-1} (25)	1.7×10^{-2} (0)
34 Fe(C_3Cap)(1,2-Me_2Im)[b]	1.4×10^{-1} (25)	3.0×10^{-2} (0)
Base concentration		
32 Fe(C_2Cap)(1,2-Me_2Im)[b]	2.0×10^{-1} (25) base = 1.0 M	2.8×10^{-1} (25) base = 0.0275 M
Solvent	$P_{1/2}^{CO}$ (°C)	$P_{1/2}^{O_2}$ (°C)
3 Fe(Chel-ProtoP)	2.5×10^{-4} (20)[c]	5.6 (20)(benzene)[c]
	1.0×10^{-3} (20)[d]	1.0 (20)(water)[d]
4 Fe(Chel-MesoP)	5.0×10^{-4} (20)	2.8 (22)(90:10 tol/CH_2Cl_2)[e]
		5.7×10^{-1} (22) (CH_2Cl_2)[f]
		3.3×10^{-1} (22) (DMF)[f]
		2.2×10^{-1} (22) (2:1 DMF/H_2O)[f]
		3.2×10^{-1} (22) (H_2O)[f,g]
5 Fe(py-chel-MesoP)[f]		9.8×10^{-1} (22) (toluene)
		8.4 (22) (DMF)
		4.4 (22) (DMF/H_2O 2:1)
		6.1 (22) (H_2O)[g]
2 Fe(T(o-OMeP)P) (1,2-Me_2Im)[b]		5.3 (−45) (toluene)
		4.1×10^{-1} (−45) (DMF)
31 Fe(C_2Cap)(1-MeIm)[b]	7.6×10^{-4} (0)	7.8×10^{-1} (−23), 4.5 (0) (toluene)
	3.0×10^{-4} (0)	3.5×10^{-1} (−23), 5.0 (0) (THF)
	—	8.2×10^{-1} (−23), 6.5 (0) (CH_2Cl_2)
	2.8×10^{-4} (0)	2.3×10^{-1} (−23), 3.3 (0) (DMF)
12 Fe($Piv_3$5ClmP)	2.2×10^{-5} (25)[i]	5.8×10^{-1} (25)[h] (toluene)
	3.0×10^{-5} (25)[i]	5.9×10^{-2} (25)[i] (1:1 toluene:MeOH)
Co(TpivPP)(1-MeIm)[j]		1.4×10^{2} (25) (toluene)
		4.3×10^{2} (25) (1:1 toluene:MeOH)
		2.2×10^{2} (25) (61:39 toluene:DMA)

TABLE III *(continued)*

Solvent	$P_{1/2}^{CO}$ (°C)	$P_{1/2}^{O_2}$ (°C)
Co(ProtoP)(1-MeIm)[k]		4.2×10^2 (−23) (toluene) 1.2×10^2 (−23) (DMF)

[a]See footnote (a) to Table I.

[b]Reference 35. Estimated errors ±10% except for oxygenation of capped porphyrins where it is ±5%.

[c]Reference 28. See also footnote (c) Table I.

[d]Reference 33. 2% aqueous myristyltrimethylammonium bromide suspension at pH 7.3.

[e]Reference 30.

[f]Reference 31. We do not find a value for the solubility of CH_2Cl_2 in the reference referred to (Ref. 48). See footnote (a) of Table I.

[g]Several values for the solubility for O_2 in toluene exist. H_2O refers to a 2% aqueous suspension of cetyltrimethylammonium bromide at pH 7.3. See also Ref. 30 for another set of values for the aqueous systems and footnote 44.

[h]Reference 40. [i]Reference 38.

[j]Reference 68. Toluene/methanol and toluene/dimethylacetamide mixtures have approximately the same dielectric constant.

[k]References 45 and 67.

coefficients and affinity constants measured at 20–25°C, whether measured on protein or on model systems, and the inferences drawn therefrom need not pertain to the physiologically more relevant temperature of 37.4°C.

Second, there is a small but apparently significant effect of increasing base concentration upon the affinity for CO of Fe(C_2Cap)(1,2-Me_2Im), **32,** at 25°C in toluene.[35]

Third, there has been much discussion that dioxygen uptake is more sensitive than carbon monoxide uptake to solvent polarity. We do not consider that this has been *convincingly* demonstrated, at least for systems at ambient temperatures. While there is a solvent effect for the binding of O_2 to Co(ProtoP)(1-MeIm) *at* $-23°C$ [$P_{1/2}^{O_2} = 417$ Torr in toluene ($\varepsilon = 2.4$) versus 12.6 Torr in DMF ($\varepsilon = 36.1$)][45,67] this difference need not pertain at ambient temperatures. Various results relevant to solvent effects for CO and O_2 binding to iron porphyrinato systems are listed in Table III. The capped and picket-fence porphyrins, notwithstanding an apparently well protected O_2 and CO binding site,

both show a substantial increase in CO affinity for solvents of increased polarity. The O_2 affinity of the iron picket-fence porphyrin shows a similar trend, but the O_2 affinity of the capped porphyrin at 0°C is essentially independent of solvent polarity. For the solvent accessible flat-open porphyrins a change in O_2 affinity of at most an order of magnitude is observed while a decrease in CO affinity of about the same magnitude occurs with different solvents. For the cobalt picket-fence porphyrin increasing solvent polarity leads to *decreased* O_2 affinity[68]—curiously contrary to O_2 binding by an iron(II) picket-fence porphyrin derivative. Whereas Co(TpivPP)(1-MeIm) binds $O_2 \sim 300$ times better than Co(T(p-OMe)P)(1-MeIm),[69] the analogous ratio between Fe($Piv_3$5CImP) (**12**) or Fe(TpivPP)(1-MeIm) (**15**) and Fe(Chel-ProtoP) (**3**) is only about 10 (see Table IV). It has been noted[28] that

TABLE IV
Comparison of dioxygen binding (in Torr) by cobalt and iron porphyrins[a]

	Compound	Reference	$P^{O_2}_{1/2}$ (25°C)	$N = P^{O_2}_{1/2}(Co)/P^{O_2}_{1/2}(Fe)$
12	Fe($Piv_3$5CImP)	b	0.58	2.4×10^2
	Co(TpivPP)(1-MeIm)	b	1.4×10^2	
	Fe(TpivPP)(1-MeIm) solid state	b	0.49	1.2×10^2
	Co(TpivPP)(1-MeIm) solid state	b	61	
31	Fe(C_2Cap)(1-MeIm)	c	23	$>6.1 \times 10^3$
	Co(C_2Cap)(1-MeIm)	c	1.4×10^5	
3	Fe(Chel-ProtoP)	d	5.5	
	Co(ProtoP)(1-MeIm)	e	1.8×10^4	$\lesssim 3.2 \times 10^3$
	Co(T(p-OCH_3P)P)(1-MeIm)	f	1.5×10^4	
32	Fe(TpivPP)(1,2-Me_2Im)	b	38	24
	Co(TpivPP)(1,2-Me_2Im)	b	9.0×10^2	

[a]Toluene solution except where noted. With the exception of the picket-fence porphyrin systems $P_{1/2}$ values are calculated from thermodynamic values.

[b]References 40 and 68.

[c]Reference 34. The Co value is at 15°C. N is therefore a minimum value.

[d]Reference 28. Temperature 20°C for Fe(Chel-ProtoP). N is therefore a maximum value. At worst an error of 30% is introduced. For O_2 binding by Fe(Chel-ProtoP) in 2% aqueous MTAB at pH 7.3 values for $P_{1/2}$ of 1.0 Torr (20°C) and 1.4 Torr (25°C) were obtained.[29]

[e]Reference 98; value extrapolated to 25°C.

[f]Reference 69; value extrapolated to 25°C.

upon change of solvent the partition coefficient $M_K = K(CO)/K(O_2)$ (K in concentration units) may increase from 3×10^2 to 5×10^3.

Fourth, it has been shown recently that for the chelated hemes, meso-(two ethyl substituents), proto-(two vinyl substituents) and acetylheme (two acetyl substituents), there is a range of about 10 in O_2 affinities and essentially none in CO affinities at 20°C in 2% MTAB aqueous suspension.[33] The partition coefficient M may vary from 2.7×10^2 to 6.2×10^3 as a function of pyrrole substituent. Similar effects have been observed for horse heart Mb reconstituted with a variety of hemes ($M = 1.1 \times 10$ for mesoheme to $M = 1.9 \times 10^2$ for 2,4-diformylheme[70]), although the different $P_{1/2}^{O_2}$ values for 2-vinyl-4-formyl- and 2-formyl-4-vinylheme and the high affinity for CO and O_2 of deuteroMb indicate that electronic effects are not the only factors determining affinities and partition coefficients. The assumption that the activity coefficients of micellized chelated proto-, meso- and diacetylheme are identical remains largely untested.[71]

For Co(T(p-X-P)P)(B) systems[72] base binding in toluene at 25°C is enhanced by electron withdrawing *para* substituents X on the phenyl rings ($\rho = 0.168(13)$ for B = pyridine in the Hammet σ–ρ relationship) whereas dioxygen binding at 20°C to such complexes is enhanced by electron donating substituents ($\rho = -0.056$, derived by extrapolation of ρ values obtained at -72, -56.5 and -38°C). However, in butyronitrile solvent dioxygen binding, which at low temperatures is favored by electron donating substituents, becomes favored by electron withdrawing substituents upon extrapolation of ρ values to 20°C ($\rho = +0.04$).

Fifth, relative to axial bases such as substituted pyridines and amines, imidazoles enhance the affinity of five-coordinate complexes for dioxygen more than might be expected from their basicities. This has often been ascribed to supposed π-donor properties of imidazoles as contrasted with pyridines,[34,73–79] although the genealogy of this rationale is uncertain.[79–84] An alternative explanation lies in a lowered steric requirement of the five-atom imidazole ring compared with the six-atom pyridine ring in six-coordinate complexes that simply permits a closer Fe–N separation and a stronger σ bond. These steric requirements have been noted in another context by Scheidt.[85] Because they are more numerous and also because of their greater physiological relevance to the hemoglobins, where the imidazole-containing histidine residue pro-

vides the fifth ligand, we will largely restrict this Comment to imidazole-containing systems.

These examples demonstrate that great care must be taken in drawing conclusions about general trends in O_2 and CO binding since the data depend on temperature, axial base concentration, solvent polarity, porphyrin and axial base. If one bears this in mind, there are rather few data that may be validly compared using the significance limits adopted above. The comparative data of Table I were selected for the following reasons:

1. Benzene or toluene was used as the solvent. These we must assume are identical with respect to their role in CO or O_2 binding.

2. Experiments were performed in the range 20–25°C.

3. Tetraphenylporphyrin-based systems and protoporphyrin-based systems are regarded as only approximately the same. The tail-under porphyrins ($Piv_3$5ClmP, **IIIb,** and Chel-ProtoP, **IVb**) are assumed to be identical with their parent picket-fence (TpivPP) and protoporphyrin IX dimethyl ester (ProtoP) species, respectively. That is, we assume (with some risk) that the tail is neither strained nor transmits strain to the porphyrin ring.

4. 1-Substituted and 1,5-disubstituted imidazoles are taken to be identical, although 1,5-dicyclohexylimidazole is a slightly stronger base than 1-methylimidazole.[35] 1,2-Dimethylimidazole and 2-methylimidazole are also taken to be approximately identical since the greater basicity of 1,2-Me_2Im[35] is in part counterbalanced by its greater steric encumbrance.[41]

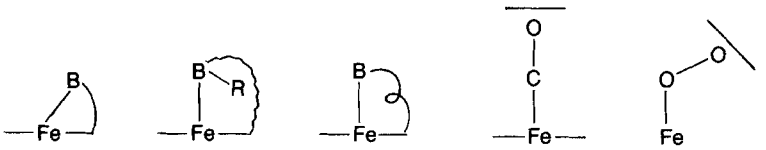
FACTORS INFLUENCING DIOXYGEN AND CARBON MONOXIDE BINDING TO IRON

Ligand binding to iron(II) porphyrinato systems involves many sometimes counterbalancing factors, as has been alluded to earlier. These may be loosely divided into electronic and steric effects. The former refer to bonded interactions, for example the substituent effects described in the last section in another context and porphyrin–solvent interactions with π acceptors and donors including toluene.[69,86–89] These effects are small in comparison with those responsible for the enormous range in ligand affinities documented in the tables. Steric effects on the

other hand involve nonbonded interactions. For example, dioxygen binds less avidly to five-coordinate Fe(Por)(B) species when B = 1,2-Me_2Im rather than 1-MeIm. Substituents attached to the porphyrins, such as pickets (**III**), caps (**V**) or straps (**VI**) may force ligands to adopt a less favored geometry, although elements of this argument, to which we will return later, have been disputed.[4]

Distal and Proximal Effects

Recently terms have been used to portray various steric influences and strains that may perturb the binding of dioxygen and carbon monoxide to Fe(Por)(B) compounds. Proximal effects (**VIII-X**) purport to affect the stereochemistry and binding of the axial base, usually an imidazole species, and hence, indirectly, the O_2 and CO affinities.[4,26] However, in view of the known conformational flexibility of porphyrins, the types of strain engendered by appropriate chain lengths (**VIII**) and chain substituents (**X**) may well be dissipated by conformational changes in the porphyrin. With respect to O_2 or CO binding these proximal effects may be considered in part electronic, since weakened base binding may result in reduced π-electron density available for delocalization from the metal atom onto the sixth ligand. Distal effects[27] are offered in the biological system by the protein and in model systems by porphyrin substituents (for example, cap,[17,34–36,90,91] picket,[3,5–8,16,37–41] diporphyrin,[43] lacunar,[92] straps[28,43,93,94] and micellar[4,26–33]). A central steric effect (**XI**) should lower carbon monoxide affinity relative to dioxygen since the former prefers to bind in a linear manner,[9] while a peripheral



ring face springboard central peripheral

VIII **IX** **X** **XI** **XII**

Proximal effects Distal effects

steric effect (**XII**) should lower dioxygen affinity since dioxygen adopts an end-on bent geometry.[7,8]

Molecular Reorganization

Upon coordination molecular reorganization may occur so that a balance is struck between maximum ligand binding (electronic) and minimum nonbonded intramolecular repulsions. Such reorganization must occur for the coordination of CO to capped porphyrin species. The C_2-Cap compounds, $H_2(C_2Cap)$[90] and $FeCl(C_2Cap)$,[91] show a porphyrin-cap separation of less than 4.0 Å, a separation much too close to allow a linear, perpendicular geometry for coordinated CO.

Solvation Energy Effects

An important steric factor, the energetics of which remain generally unknown, involves the reorganization of the solvent cage upon ligand binding. This point, which has been argued in depth,[32,38] is discussed also in the next section. For the picket-fence porphyrin complexes Fe(TpivPP)(2-MeIm) and Fe(TpivPP)(2-MeIm)(O_2) this effect should be small since changes in molecular bulk have been shown to be small, at least in the solid state.[7] The pickets and porphyrin change their conformation insignificantly; the major change is the 0.31Å movement by the 2-MeIm group towards the porphyrin plane, resulting in a small decrease in molecular bulk. For Fe($Piv_3$5ClmP) a somewhat larger movement (i.e., ~ 0.4 Å) could be expected in the absence of the 2-methyl substituent. On the other hand, for the ligation of O_2 by Co(TpivPP)(1-MeIm) a movement of only ~0.1 Å could be expected by analogy to the structures of five-coordinate Co(II) and six-coordinate Co(III) complexes[12]—a much smaller decrease in molecular bulk. Herein may lie an explanation for the curious *decrease* in O_2 affinity of Co(TpivPP)(1-MeIm) in solvents of *increased* polarity. The cobalt derivatives of flat-open porphyrins and possibly of capped porphyrins also show a marked aversion to dioxygen binding compared with the cobalt derivatives of the picket-fence porphyrins, as shown by the values of $N = P^{O_2}_{1/2}(Co)/P^{O_2}_{1/2}(Fe)$ in Table IV.[28,29,34,40,68,69,95–98] These differences may originate in solvation energy effects. The distinction between solvent polarity effects and solvation energy changes upon ligation has not always been clearly defined.[32] In any event, that there are small, large,

or medium solvent polarity effects upon CO or O_2 binding does not imply that solvation energy changes accompanying such binding are small, especially for the flat-open porphyrins where there is a substantial change in the conformation and bulk of the complex.

Other Steric Effects

These are by no means the only steric influences upon ligand binding. Hydrogen bonding, dipole–dipole interactions and intramolecular solvating of coordinated ligands may also perturb ligand affinities. Such effects and others have been examined[5] in connection with how some hemoglobins, such as Hb *Ascaris*, may achieve affinities for O_2 far greater than those yet observed for any model systems.

Intrinsic Affinity

A fundamental problem remains, however, in assigning and identifying various steric effects. Some notion of the intrinsic affinity for O_2 and CO of some five-coordinate iron porphyrinato moieties is presupposed. A conceptually useful if physically unobtainable reference point, where perturbation of the affinity by solvent and distal effects is absent, is provided by the molecules Fe(TPP)(1-MeIm) or Fe(chel-ProtoP) in the gas phase. Collman et al.[38] have discussed in detail the assumptions made in equating the intrinsic solvent-independent equilibrium constant for the gas phase K_g with the equilibrium constants in solution measured in terms of pressure K_p and concentration units K_c of the gaseous sixth ligand L. The equilibria involved are

$$\mathrm{Fe(Por)(B)_g} + \mathrm{L_g} \overset{K_g}{\rightleftharpoons} \mathrm{Fe(Por)(B)(L)_g};$$

$$K_g = \frac{P\{\mathrm{Fe(Por)(B)(L)}\}}{P\{\mathrm{Fe(Por)(B)}\}P\{\mathrm{L}\}};$$

$$\mathrm{X_g} \overset{K_s\{\mathrm{X}\}}{\rightleftharpoons} \mathrm{X_s};$$

$$K_s\{\mathrm{X}\} = \frac{P\{\mathrm{X}\}}{[\mathrm{X}]},$$

where Fe(Por)(B) is a five-coordinate iron(II) porphyrinato complex with a nitrogenous axial base B, and $P\{\mathrm{X}\}$ is the partial pressure of

some species X = Fe(Por)(B), Fe(Por)(B)(L), or L. The former assumption, $K_p = K_g$, holds if

$$K_s\{\text{Fe(Por)(B)(L)}\} = K_s\{\text{Fe(Por)(B)}\}.$$

The latter assumption $K_c = K_g$ implies

$$K_s\{\text{Fe(Por)(B)(L)}\} = K_s\{\text{Fe(Por)(B)}\}K_s\{\text{L}\}.$$

For the picket-fence porphyrins and hemoglobins, where molecular bulk *decreases* only a small amount upon oxygenation or carbonylation and where the ligand is not in contact with the bulk solution, the assumption $K_p = K_g$ may be tenable since the solvation energies of Fe(Por)(B)(L) and Fe(Por)(B) should be similar. For flat-open porphyrins and possibly for the carbonylation of Fe(C_2Cap)(1-MeIm) this assumption is untenable, as molecular bulk *increases* substantially upon ligation. In general the use of K_c seems worthless insofar as it indicates intrinsic properties free of solvation effects. Thus, a host of factors that contribute to the free-energy change upon coordination of CO or O_2 may be summarized (or hidden) in the measured quantity $P_{1/2}^{CO}$ or $P_{1/2}^{O_2}$.

$$\begin{aligned}\Delta G = \Delta G^{\text{elec}}_{\text{binding } O_2} &- \Delta G^{\text{steric}}_{\text{hydrogen bonding}} \\ &- \Delta G^{\text{steric}}_{\text{intram. solvation}} \\ &+ \Delta G^{\text{steric}}_{\text{distal effects}} \\ &+ \Delta G^{\text{steric}}_{\text{molecular reorg}} \\ &+ \Delta G^{\text{steric}}_{\text{solvent reorg}}\end{aligned}$$

This separation is to some extent artificial: for example, a molecular reorganization of a cap to accommodate a ligand may be limited by concomitant solvent reorganization, a variation of the chicken–egg conundrum. Nonetheless, the above equation highlights again the care required in selecting systems for comparison.

ANALYSIS OF THE DATA IN TABLE I

Systems that display anomalies, suggestions for analyzing the data in Table I and a number of factors that influence ligand binding have been described. We now focus on the data of Table I, particularly on those

systems that show a relative discrimination against O_2 or CO ligation. With strict attention to the conditions delineated in Table I, the following broad categories may be defined:

For $M > 2 \times 10^4$, relative discrimination in favor of CO;
For $M < 2 \times 10^2$, relative discrimination in favor of O_2.

We now examine the various types of porphyrin species for the structural basis of the relative discriminations observed. In particular, peripheral steric effects, which might favor CO ligation, and central steric effects, which might favor O_2 ligation, are discussed. Bear in mind that these model systems all have a much lower affinity for dioxygen than some of the hemoglobins documented in Table II.

The Capped Porphyrins

The relative discrimination of the Fe(C_2Cap)(1,2-Me_2Im) system (**32**) in favor of CO ligation has been rationalized[36] in terms of a peripheral steric effect between O_2 and the atoms of the chains to the cap, an effect that is absent for CO ligation. This description may be flawed. Unless the cap is markedly off-center, for which there is no evidence yet, the closest contacts are between the phenyl cap and the ligand L for both L = O_2 and CO. The structures observed for two crystalline derivatives[90,91] as well as model building indicate an unsuspected conformational variability in the chains that attach the cap to the tetraphenylporphyrin. That equilibrium for oxygenation of compounds **31–38** is established rapidly compared with equilibrium for carbonylation[35] suggests that the carbon monoxide derivatives have conformations very different from those of the parents and their oxygenated adducts. If the conformations differ sufficiently—either through differences in strain energy or molecular bulk—so that the CO and O_2 adducts are no longer comparable systems, then the concept of relative discrimination has no meaning.

For the C_2Cap systems, as well as other systems in Table I where comparisons can be made, the substitution of 1,2-Me_2Im for 1-MeIm disfavors both CO and O_2 ligation. The data do not enable us to conclude that this substitution has a significant effect on M.

Other interesting features in the ligand binding by the capped porphyrins may be found. First the C_3Cap species **33** and **34** bind CO with an affinity (at 25°C) similar to the C_2Cap species **31** and **32**, respectively. On the other hand, for O_2 binding (at 0°C) there is a significant difference

in affinity between C_2Cap species **31, 35,** and **37** ($P_{1/2}^{O_2}$ = 4.5, 2.3 and 7.1 Torr, respectively) and C_3Cap species **33** ($P_{1/2}^{O_2}$ = 54 Torr). That Fe(C_3Cap)(1-MeIm) can bind a second 1-MeIm molecule, albeit more weakly than the first[34] (flat-open porhyrins bind the second more strongly), provides further evidence for conformational flexibility of capped porphyrins. Differences in CO affinity at 25°C among C_2Cap, NapC_2Cap and C_2Cap-NO_2 species are also insignificant ($P_{1/2}^{CO}$ = 5.4 × 10^{-3}, 2.9 × 10^{-3} and 7.0 × 10^{-3} Torr for **31, 35,** and **37,** respectively; $P_{1/2}^{CO}$ = 2.0 × 10^{-1}, 1.0 × 10^{-1} and 5.1 × 10^{-1} Torr for **32, 36,** and **38,** respectively).

The Flat-Open Porphyrins

The flat-open porphyrin **3** also shows an apparent relative discrimination in favor of CO ligation. It is conceivable for the flat-open porphyrin systems **1–4** that the linearly bound CO adduct allows better porphyrin solvation than the angularly bent and more bulky O_2 adduct. In any event, the different affinities of the flat-open porphyrins and the picket-fence porphyrins—where, as discussed earlier, solvent reorganization upon ligation is much smaller—may give some indication of the magnitude of solvation energy changes. The $P_{1/2}^{O_2}$ value for **12** is 0.58 Torr, while that for **3** is 5.5 Torr. This corresponds to ~1.5 kcal/mol. The $P_{1/2}^{CO}$ value for **12** is 2.2 × 10^{-5} Torr, that for **3** is 2.5 × 10^{-4} Torr. Since the former measurements were at 25°C and the latter at 20°C this difference represents a lower bound.

The Picket-Fence Porphyrins

The binding of CO to the Fe(picket-fence) compounds **11** and **12** has been described, not for the first time,[4] as anomalous.[36] We wish here to advance the hypothesis that the picket-fence porphyrins in fact constitute a system that offers a very substantial discrimination against O_2 binding, and further, one that allows more or less unconstrained CO binding. Relative to the capped porphyrins (entries **31–38** at 25°C) the picket-fence porphyrins (entries **11** and **12**) exhibit a much higher CO affinity (>10^2) and a somewhat higher O_2 affinity (~10^1), although the difference in M values for the 1-MeIm derivative is only sixfold and thus not significant. Using the coordinates from the structures of Fe(TpivPP)(2-MeIm)(O_2)[7] and its 1-MeIm analogue[8] and assuming the

Fe–CO stereochemistry found for Fe(TPP)(py)(CO)[9,99] we have calculated and compared CO and O_2 contacts with atoms of the pickets. Although these atoms have high thermal motion or unresolvable disorder or both, there is little doubt that close contacts between methyl groups and the terminal oxygen atom, inescapable for the dioxygen ligand, do not occur for our hypothetical carbon monoxide structure (see Table V). Thus, these substantial peripheral oxygen–methyl contacts may be an important factor in bestowing on **12** dioxygen affinity ($P_{1/2}^{O_2}$ = 0.58 Torr) that is lower than that for many hemoglobins. On the other hand, the carbon monoxide affinity is higher than in any other system, ($P_{1/2}^{CO}$ = 2.2×10^{-5} Torr, either model or biological, because at least for the model system there is here a demonstrated absence of peripheral and central steric interactions.

Substitution of 1,2-Me_2Im for 1-MeIm lowers both the O_2 and CO affinities by similar factors, thus leaving M more or less unaltered (entry **12** versus **11**). The structural manifestations of this change have been characterized.[7,8] Whereas for the 1-MeIm derivative the Fe atom is in the plane of the porphyrinato nitrogen atoms and the Fe–O bond is 1.75(2) Å, for the 2-MeIm compound the Fe atom is displaced 0.086 Å toward the 2-MeIm ligand and the Fe–O and lengthens to 1.898(7) Å.

The Fe(PocPiv) compounds **13** and **14** show an O_2 affinity marginally

TABLE V
Intermolecular contacts (Å) between the terminal oxygen atom and the methyl groups for O_2 and CO adducts of the picket-fence porphyrin

Fe(TpivPP)(2-MeIm)		Fe(TpivPP)(1-Me)	
O_2	CO[a]	O_2	CO
2.77(3)	3.46	2.67(6)	3.23
2.98(3)	3.59	3.07(6)	3.55
		3.07(6)	3.60
		3.14(6)	3.57

[a]Calculated on the assumption that Fe–C and C–O separations are 1.77 Å and 1.15 Å and that the CO group lies on the twofold axis. For the CO complex the Fe atom is at the same position as in the O_2 complex. Any error in O(CO) methyl contacts is at most 0.07 Å; in Fe(TpivPP)(1-MeIm)(L), the Fe atom is −0.03 Å from the plane towards the imidazole ligand for L = O_2,[8] and for L = CO the distance is taken to be zero.

higher than that for the comparable Fe(TpivPP) complexes for both 1-MeIm and 1,2-Me_2Im bases. However, CO affinity is reduced by *two orders* of magnitude. Thus the *M* values, which are 4.3×10^3 and 2.2×10^4 for **11** and **12,** are only 2.7×10^2 and 2.2×10^2 for **13** and **14.** Recall that CO may bind to **11** and **12** without steric clash and with little molecular reorganization, and that the coordinated CO is buried inside the binding pocket. Since the change in porphyrin has affected only the CO affinity and since the porphyrins are electronically very similar (see **IIIa** and **IIIc**) this constitutes strong evidence for a central steric effect.

Now, if the picket-fence porphyrin presents a relatively unconstrained environment for CO binding, why is its apparent affinity more than an order of magnitude greater than that for a flat-open porphyrin (see Table I) which also presents an apparently unconstrained environment? The answer probably lies in solvation energy effects.[38] With the highly enclosed pocket and negligible changes in conformation and bulk of the complex upon coordination of CO or other ligands, ligand binding by the picket-fence porphryin should be relatively unperturbed by solvation energy effects, as suggested earlier[38] and confirmed by the structures of Fe(TpivPP)(2-MeIm) and its dioxygen derivative.[7] The binding of CO to **11** and **12** in toluene is probably the best approximation to the intrinsic affinity for CO of these porphyrins or any other porphyrin in the absence of solvation energy effects.

Strapped and Cyclophane Porphyrins

The affinity for both CO and O_2 of the cyclophane porphyrins **21** and **22** (see diagram **VI**) is very sensitive to the strap length. A change of more than two orders of magnitude occurs on shortening the strap. However, no pronounced discrimination effects were observed and the conclusion was reached, at least for such systems and dioxygen-transporting hemoproteins, that CO and O_2 are not differentiated by steric effects.[28] Compared with the rigid lacunar species (**VII**) and the pocket picket-fence porphyrins, the cyclophane compounds **21** and **22** with their two points of attachment may show conformational flexibility that could lead to different solvation energy effects on the binding of CO versus O_2. On the other hand, the strapped porphyrin **25** does discriminate against CO ($M = 3.0 \times 10^2$). Whether this arises from a central steric effect or from conformational changes upon ligation is unknown.

Diporphyrins

Discrimination against CO is also observed in the compounds **41** and **43.** In the dicopper species the intraring separation is estimated by ESR methods to be ~3.8 Å.[43] If this separation obtains in the FeCu complexes then conformational changes upon ligation must occur and a central steric effect would be only apparent.

Lacunar Compounds

Although not documented in Table I because the macrocycle is nonporphyrin and nonanionic, iron(II) derivatives of these species (**VII**) also show that distal steric effects may perturb O_2 and CO binding.[92] Indeed the crystal structure of one derivative shows that the Fe–CO bond is slightly bent [170.6(5)°] and noticeably tilted away from the perpendicular to the macrocycle plane. The authors conclude that "CO affinity is more sensitive to steric effects than is O_2 affinity."[92]

CONCLUDING REMARKS

It has only been a decade since the first measurements of O_2 affinity of cobalt porphyrin systems were made and only eight years since the O_2 affinities of comparable iron porphyrin systems were measured at low temperatures and the first of the highly modified iron porphyrins, capable of withstanding irreversible oxidation at higher temperatures, was synthesized. These models have been among the more successful of those developed to probe coordination sites in metallobiomolecules.[100] They have been especially successful as structural models, providing excellent benchmarks against which the results of structural studies of the heme groups in proteins may be judged.[5]

In this Comment we have tabulated selected published data on the binding of O_2 and CO to these model iron porphyrin systems. The various compounds differ in a number of ways, including shape, rigidity, ligand affinities and relative discrimination of O_2 versus CO. The interpretation of these data consequently poses a fascinating problem in inorganic chemistry, one that is made even more exciting by the knowledge that what is learned will ultimately be of great significance to our

understanding of structure–function relationships in vertebrate hemoglobins. Unfortunately, interpretation of these data is not straightforward. Although we have pointed to a number of trends and interesting effects, we offer no tidy final summary since a global view over noncomparable systems is difficult. Rather it seems to us that an understanding of the ligand binding properties of these systems will ultimately rest on a number of additional experiments. Here are a few examples. (1) The number of solid-state structures of these compounds is very limited. We have entire classes of models, for example the caps and straps, where no structural data on the O_2 or CO adducts are available. We thus have no direct information on the conformational changes that occur on ligation. Clearly accumulation of further structural data is essential. (2) Such solid-state structures when available must be related to structures in solution where ligation occurs. The problem of relating solid-state and solution structures is one that pervades much of chemistry. In this regard new NMR techniques, including magic angle spinning, offer some hope. (3) The present information on ligand binding is largely in the form of $P_{1/2}$ values, although more complete thermodynamic data are sometimes available. Our understanding of the factors that affect binding and the mechanisms involved would be considerably enhanced if rate data were available. (4) A number of factors, including solvation energy effects, remain essentially unexplored and ways must be found to probe these. In particular, calorimetric studies of ligand binding and studies of solute nonideality for five- and six-coordinate species would prove very helpful. (5) Although Nature has succeeded in producing high-affinity hemoglobins, chemists have not. This presents a challenge, one that will probably be met only through difficult organic syntheses, of producing models that show ligand binding characteristics greatly enhanced over those presently observed. The existence and characterization of such models would aid considerably in understanding both the models and the biological systems.

Thus, the synthesis and characterization of metalloporphyrin systems that bind O_2 and CO and the measurement and interpretation of their binding properties are problems at the forefront of modern inorganic chemistry. To solve these problems will require measurements and interpretations from diverse areas of inorganic chemistry. But the significance of what is learned will extend well beyond inorganic chemistry to crucial areas of protein biochemistry.

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for CO binding to chelated protoheme in 2% phosphate-buffered MTAB solution at pH 7.3 and 20°C of 7.2 × 10^8 derived from k_{on} = 3.6 × 10^6 M^{-1} s^{-1} and k_{off} = 0.005 s^{-1} (Table III referring to Ref. 33 where these values may indeed be located; error ±10%) and of 4 × 10^8 (Table I, referring to Ref. 29; from k_{on} = 3.6(1) × 10^6 M^{-1} s^{-1} and k_{off} = 0.0089 s^{-1}). The value for k_{off} may come from Table VI in Ref. 32 for a cetyltrimethylammoniumbromide, CTAB (1.6%), and MTAB (0.4%) mixture. A value of 0.0079 s^{-1} (error ±10%) in a 2% CTAB suspension may also be found in Table IV of Ref. 32. From a probable value for the CO solubility in benzene (9.97 × 10^{-6} M/Torr[28]), the value for K_{CO} of 4 × 10^8 M^{-1} by the chelated protoheme in benzene at 20°C reported in Ref. 4 (which probably originates from Ref. 28) yields a value of 0.00025 Torr. (The stated value is 0.0004). We hope that we have chosen the intended values for inclusion in our Tables I and III.

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second base-off pathway may complicate data analysis, are not available. In a number of picket-fence porphyrin systems equilibrium for ligand binding has been approached from both sides (B. Iverson, personal communication). This approach certainly increases precision and possibly accuracy as well. Ideally we would like to see measurements duplicated in different laboratories, analogous to those frequently encountered in the literature on hemoglobins. This would provide greater confidence in the accuracy of the measurements.

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