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Kinetics and Thermodynamics of Oxygen and Carbon Monoxide Binding to Simple Ferrous Porphyrins at Low Temperatures

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Abstract: The results of detailed kinetic and thermodynamic studies of oxygen and carbon monoxide binding to simple ferrous porphyrins are reported. In methylene chloride at −79° $Fe(TPP)(base)_2$ (where base = pyridine, piperidine, and 1-methylimidazole and TPP = *meso*-tetraphenylporphyrin) reacts with oxygen and carbon monoxide in a manner consistent with the dissociative process outlined in the following mechanism: $Fe(TPP)(base)_2 \rightleftharpoons Fe(TPP)(base) + base$; $Fe(TPP)(base) + O_2 \rightleftharpoons Fe(TPP)(base)(O_2)$; $Fe(TPP)(base) + CO \rightleftharpoons Fe(TPP)(base)(CO)$. Quantitative comparisons of O_2 and CO binding to the ferrous complexes, including the influence of the various axial bases, are discussed. Comparisons between these simple systems and natural oxygen carriers suggest that these systems may serve as satisactory models for the more complicated heme proteins. In part, the results show that if "distal" imidazole could bind to heme in the oxygen carrying proteins, it would seriously hamper the proteins' ability to function as an effective oxygen carrier.

The reactions of monomeric heme proteins (myoglobin and the isolated α- and β-chains of hemoglobin) with oxygen and carbon monoxide have been extensively studied.[1] In contrast, the reactions of simple ferrous porphyrins with carbon monoxide have received little attention,[2,3] and their reactions with oxygen have, until recently,[4] not been investigated due to irreversible oxidation of the iron center. However, such studies should be useful in elucidating the role of the protein in the reactions of hemoglobin and myoglobin with various ligands. They may even aid the understanding of structural variations which produce abnormal oxygen affinities[5] in heme proteins.

Following our recent communication on the reversible reaction of ferrous tetraphenylporphyrins with oxygen at low temperatures,[6] we have examined the detailed kinetics and equilibria of the reaction of these same ferrous porphyrins with oxygen[7] and carbon monoxide as a function of various axial bases. This study has been performed in methylene chloride at −79°. Care must be taken in comparing our kinetic parameters with those determined for the heme proteins because of the difference in temperature, and the nature of the solvent medium. However, the latter factor could be fairly similar in the two systems. Myoglobin is folded such that the heme is in a hydrophobic pocket, despite the aqueous physiological conditions surrounding the protein. Methylene chloride provides a similar hydrophobic condition.

Experimental Section

Materials. Unless otherwise specified, all chemicals were of reagent grade. Matheson prepurified nitrogen was passed through two chromous scrubbers and subsequently dried by sulfuric acid followed by KOH-Drierite. Matheson extra dry oxygen was further dried by bubbling through methylene chloride at −79°. Carbon monoxide was C.P. grade (Matheson). Prior to use, 1-methylimidazole (under reduced pressure), pyridine, and piperidine were distilled over KOH; methylene chloride was distilled over P_2O_5. *meso*-Tetraphenylporphyrinbis(pyridine)iron(II), $Fe(TPP)(py)_2$, was prepared by the method of Kobayashi and Yanagawa.[8] Anal. Calcd for $[Fe(C_{44}H_{28}N_4)(C_5H_5N)_2]$: C, 78.45; H, 4.60; N, 10.17. Found: C, 77.62; H, 3.88; N, 10.03. *meso*-Tetraphenylporphyrinbis(piperidine)iron(II), $Fe(TPP)(pip)_2$, was prepared by the method of Epstein et al.[9] Anal. Calcd for $[Fe(C_{44}H_{28}N_4)((C_5H_{11}N)_2]$: C, 77.33; H, 5.97; N, 10.02. Found: C, 78.45; H, 6.00; N, 9.73. *meso*-Tetraphenylporphyrinbis(1-methylimidazole)iron(II), $Fe(TPP)(1\text{-}Me(imid))_2$, was a generous gift from Professor J. P. Collman and Dr. R. R. Gagne of Stanford University.[10]

Analyses. Elemental analyses of C, H, and N were performed by H. Beck of this department.

Equipment. Visible and ultraviolet spectra were recorded on a Cary Model 14 spectrophotometer. The cold temperature work was performed using a Pyrex cell (W. Sales Ltd., Deerfield, Ill.) mounted in a dewar.[11] Gas chromatographic experiments were performed on a Hewlett-Packard Model 5700 A gas chromatograph connected to a H-P Model 7127 A strip chart recorder. Nitrogen and oxygen were separated on a 10 ft × ⅛ in. column of molecular sieves 5A, 60-80 mesh.

Oxygen Uptake Measurements. Oxygen uptake was determined using a 2-cm^3 gas buret at constant temperature and pressure.[12] The iron complex (30-35 mg) was added to a tared, thin-walled ampule. After determining the exact weight of the complex, the ampule was filled with clean, dry sand (to prevent it from floating) and sealed. The ampule was added to a flask containing 40-45 ml of methylene chloride and a magnetic stir bar. The flask was then attached to the gas buret, cooled to −45° and equilibrated with 1 atm of O_2. The ampule was broken by increasing the stirring rate. The mercury was then raised in the buret to maintain the pressure at 1 atm, and the resulting change in volume was measured. To calculate the O_2 uptake, it was necessary to know the effective temperature of the gas contained in the system. This was independently determined by adding a known amount of gas to the system and, while keeping the pressure at 1 atm, measuring the change in volume.

Oxygen Solubility. The solubility of oxygen in methylene chloride at −79° was determined using a constant volume vacuum line and a specially designed creased reaction flask. Oxygen absorption by solutions of CH_2Cl_2 was calculated from PVT measurements at constant volume.[13] For these calculations it was necessary to know the effective temperature of the gas. This was found by adding a known amount of gas to the system and measuring the pressure change. Since the volume of the system was known, the effective temperature could then be calculated.

For the range of oxygen pressures examined (0.15-0.95 atm), the solubility of O_2 was found to vary linearly with the partial pressure. O_2 solubility in 20.0 ml of CH_2Cl_2 at −79° equals $(9.8 \pm 0.6) \times 10^{-5}$ mol/atm of O_2.

Partial Pressure Measurements in the Cold Temperature Cell. A gas-tight syringe was the most convenient method for adding small amounts of oxygen to a solution of the ferrous complex. By determining the resulting partial pressure of O_2 above the solution, and knowing the solubility of O_2 in methylene chloride at −79° as a function of partial pressure, the resulting O_2 concentration could be calculated. Since the total volume of the cell was much larger than the volumes of oxygen introduced, the resulting partial pressure of O_2 could be approximately predicted by a linear relationship with the constant for the cell being 3.4×10^{-3} atm O_2/cm^3 of O_2 injected (for injections less than 50 cm^3). This constant was determined by syringing a known volume of oxygen into 20.0 ml of methylene chloride contained in the cold temperature cell (−79°, 1 atm of N_2). After equilibrating, samples of the gas mixture above the solution were withdrawn and injected into a gas chromatograph. From the peak areas and calibration curves, the partial pressure of O_2 was calculated for each volume of O_2 originally added to the cell.

In light of the ideal gas law and the fact that less than 1% of the added gas dissolves in the solvent, this cell constant was then used for other cases in which a gas was injected into the cell containing an atmosphere of another gas.

General Procedures. For the preparation of air-sensitive solutions at cold temperatures, approximately 0.5-1.0 mg of iron complex was added to the cold temperature cell. It was then flushed with N_2 for at least an hour, before cooling to about −60°. Using a gas-tight syringe, 20 ml of nitrogen-saturated solvent was slowly dripped down the sides of the cooled cell, and nitrogen was bubbled through the mixture for about 0.5 hr to effect dissolution. The cell was then cooled to the desired temperature and the visible spectrum recorded to confirm the presence of an iron(II) species.

Oxygen adducts were formed by bubbling prechilled oxygen through cold solutions of the iron(II) complexes. The presence of the adduct was confirmed by its visible spectrum. To determine reversibility of adduct formation, N_2 was bubbled through the solution until there was no further change in the visible spectrum. In cases of complete reversibility, the original iron(II) spectrum was regenerated.

Equilibrium Measurements. Equilibrium constants were determined at −79° using the cold temperature cell. For the equilibrium

$$Fe(TPP)(base)_2 + O_2 \rightleftharpoons Fe(TPP)(base)(O_2) + base$$

a CH_2Cl_2 solution of $Fe(TPP)(base)_2$ was prepared at −79°, and an initial spectrum was recorded under 1 atm of N_2. Oxygen was then bubbled through the solution for more than an hour, the cell sealed under 1 atm of O_2, and the spectrum of the O_2 adduct recorded. To form the equilibrium mixture, a known solution of freshly prepared base-methylene chloride was slowly injected into the solution of the oxygen adduct (the pressure above the solution remaining at 1 atm of O_2). After thorough mixing and a sufficient length of time for the reaction to reach completion, the spectrum of the equilibrium mixture was recorded.

An independent, but less accurate, determination of equilibrium constants was made by adding aliquots of air to solutions of $Fe(TPP)(base)_2$. Spectral changes were monitored as described above.

To determine the lower limit for the constants describing the equilibrium

$$Fe(TPP)(base)_2 + CO \rightleftharpoons Fe(TPP)(base)(CO) + base$$

a solution of $Fe(TPP)(base)(O_2)$ in CH_2Cl_2 at −79° was prepared and sealed under 1 atm of O_2. The initial spectrum was recorded, a known volume of CO injected into the cell, and the reaction monitored spectrally until it had reached completion. Finally the spectrum of Fe(TPP)(base)(CO) was recorded under 1 atm of CO.

Kinetic Measurements. Kinetic measurements were made in methylene chloride at −79° using the cold temperature cell. For the forward reaction, solutions of $Fe(TPP)(base)_2$ ($1.4\text{-}6.6 \times 10^{-5}$ *M*) were prepared in 20.0 ml of CH_2Cl_2 under 1 atm of N_2. Known volumes of O_2, air, or CO were injected into the solution and the resulting growth in absorption at 547 nm was monitored spectrophotometrically. It was also possible to follow the reaction at 580 nm, the observed rate constant being independent of wavelength employed. The usual plots of log $(A_t - A_\infty)$ vs. time were linear for at least 95% of the reaction.

For the reverse reaction, $Fe(TPP)(base)(O_2)$ was prepared by bubbling oxygen through the solution of the ferrous porphyrin for at least an hour. Then 1.0 ml of a freshly prepared base-methylene chloride solution was slowly injected while O_2 still bubbled through the solution to ensure thorough mixing. (To prevent interference from the hydrochloride salt of the particular base, the base-methylene chloride solution must be used immediately after preparation.) The cell was subsequently sealed under 1 atm of O_2 and the decay in absorption monitored at 547 nm. Again, the plots of log $(A_t - A_\infty)$ vs. time were linear for at least 95% of the reaction.

For the reaction of $Fe(TPP)(base)(O_2)$ with CO, a procedure was followed which combined the appropriate techniques outlined above.

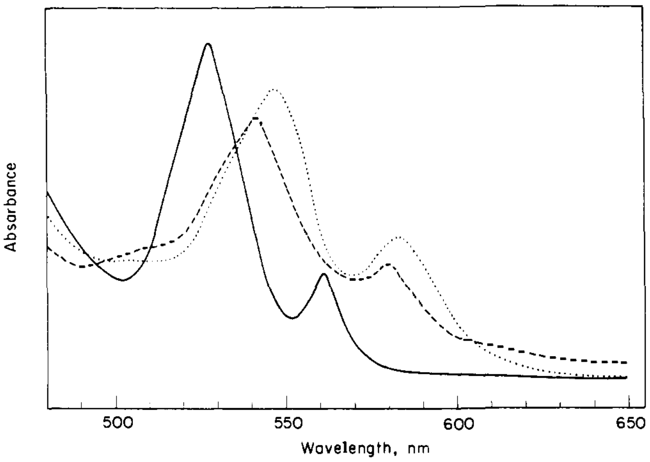

Figure 1. Visible spectra of Fe(TPP)(py)$_2$ (—) under nitrogen, Fe(TPP)(py)(O$_2$) (·····) under oxygen, and Fe(TPP)(py)(CO) (-----) under carbon monoxide in methylene chloride at −79°.

For any kinetic study involving carbon monoxide, precautions were taken appropriate to the extreme light sensitivity of these reactions.

Results

Characterization of the Oxygen and Carbon Monoxide Adducts. When a −79° methylene chloride solution of Fe(TPP)(py)$_2$, prepared under nitrogen with no added pyridine, was exposed to oxygen, a color change from yellow-orange to red-orange resulted. The spectrum of the oxygenated solution was distinctly different from that of the Fe(III) monomer[14] or the Fe(III) μ-oxo dimer.[8] In the 500-600-nm region the bands of Fe(TPP)(py)$_2$ were shifted toward the red upon oxygenation (see Figure 1). If the oxygen was removed by bubbling purified nitrogen through the solution for about an hour, the spectrum returned to that characteristic of Fe(TPP)(py)$_2$. These spectral changes are very similar to those reported by Collman et al.[15] for reversible binding of dioxygen in ferrous complexes derived from a "picket fence" porphyrin. The "picket fence" complex is a substituted iron *meso*-tetraphenylporphyrin whose spectral changes should be similar to those of the unsubstituted complex.

To confirm that this spectral behavior was due to the formation of an oxygen adduct, the quantitative uptake of dioxygen by Fe(TTP)(py)$_2$ in methylene chloride was measured. These experiments were performed at −45° because of limited solubility of the metal porphyrin at −79°. (Oxygenation at −45° yields spectral changes similar to those observed at −79°.) It was found that 0.96 ± 0.10 mol of O$_2$ were taken up per mole of Fe(TTP)(py)$_2$ initially present. Hence the stoichiometry of oxygen binding shows a 1:1 oxygen adduct.

These results were not limited to the ferrous complex in which pyridine was the axial base. Oxygenation-deoxygenation cycles with spectral changes similar to the pyridine system could also be effected for Fe(TPP)(1-Me(imid))$_2$ and Fe(TPP)(pip)$_2$. (The spectra of Fe(TPP)(base)$_2$ and corresponding adducts are not significantly affected by changing the base.)

When a methylene chloride solution of Fe(TPP)(base)$_2$ was exposed to carbon monoxide at −79°, the region of the visible spectrum from 500 to 600 nm was again shifted toward the red. However, the shift was not as great as that observed upon oxygenation (see Figure 1). The spectrum can be returned to that characteristic of Fe(TPP)(base)$_2$ by purging the solution with nitrogen, while exposing it to bright light.

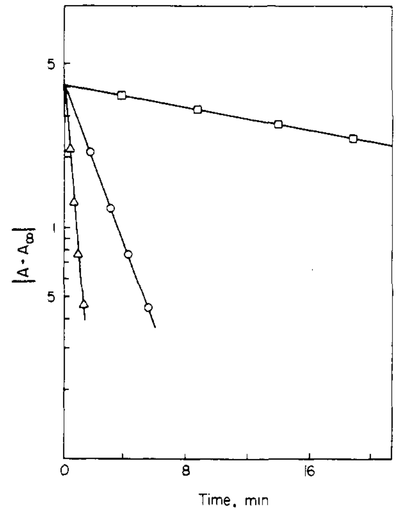

Figure 2. Plots of $|A - A_\infty|$ vs. time for the reaction of Fe(TPP)(base)$_2$ with O$_2$ in CH$_2$Cl$_2$ at −79°: ○, base = py; △, base = pip; □, base = 1-Me(imid).

Table I. Representative Kinetic Data for the Reaction of Fe(TPP)(base)$_2$ and Excess Oxygen in CH$_2$Cl$_2$ at −79°

Fe(TPP)(base)$_2$[a]	[O$_2$],[b] F	k^f_{obsd},[c] sec^{-1}
Fe(TPP)(py)$_2$	1 min bubbling O$_2$	6.2×10^{-3}
	1 min bubbling O$_2$	6.7×10^{-3}
	1 min bubbling air	6.6×10^{-3}
	3.8×10^{-4}	6.5×10^{-3}
	8.8×10^{-4}	6.8×10^{-3}
	1.8×10^{-3}	6.5×10^{-3}
Fe(TPP)(pip)$_2$	20 sec bubbling O$_2$	2.5×10^{-2}
	20 sec bubbling O$_2$	3.3×10^{-2}
	3.5×10^{-4}	2.5×10^{-2}
	1.8×10^{-3}	2.5×10^{-2}
Fe(TPP)(1-Me(imid))$_2$	10 min bubbling O$_2$	6.7×10^{-4}
	10 min bubbling O$_2$	5.8×10^{-4}
	3.5×10^{-4}	6.4×10^{-4}
	1.8×10^{-3}	5.9×10^{-4}

[a] $[\mathrm{Fe(TPP)(base)_2}]_0 = (1.4\text{–}6.6) \times 10^{-5}$ *F*. [b] The bubbling rate was 400–600 cm^3/min. [c] Estimated error ± 5%.

Kinetics. During characterization of the oxygen adducts, it was noted that the rate of adduct formation varied with the nature of the axial base. This observation was quantified by determining rate constants for the forward reaction

$$\mathrm{Fe(TPP)(base)_2} + \mathrm{O_2} \xrightarrow{k^f_{obsd}} \mathrm{Fe(TPP)(base)(O_2)} + \text{base} \quad (1)$$

The reaction was examined at −79° in methylene chloride under conditions where Fe(TPP)(base)(O$_2$) was fully formed. For each of the bases examined, Fe(TPP)(base)$_2$ disappeared in a first-order fashion (Figure 2). The results for the pyridine, piperidine, and 1-methylimidazole systems are summarized in Table I. The values tabulated indicate that, for a given complex, the rate of reaction was independent of the amount of oxygen added.

Under identical conditions, the analogous reaction with carbon monoxide was also investigated

$$\mathrm{Fe(TPP)(base)_2} + \mathrm{CO} \xrightarrow{k^{f'}_{obsd}} \mathrm{Fe(TPP)(base)(CO)} + \text{base} \quad (2)$$

When small volumes of CO (resulting [CO] ranging from 3×10^{-4} to 9×10^{-4} *F*) were syringed into the solution, Fe(TPP)(base)$_2$ no longer disappeared in a first-order man-

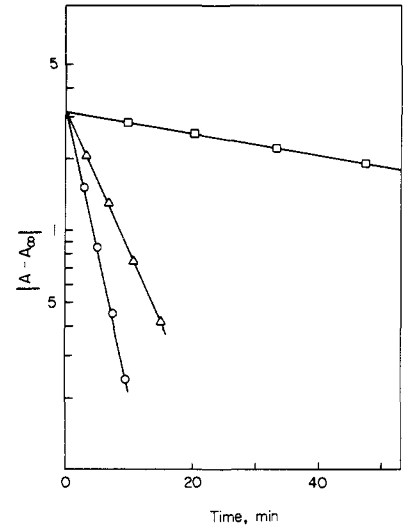

Figure 3. Plots of $|A - A_\infty|$ vs. time for the reaction of Fe(TPP)(base)(O_2) with base in CH_2Cl_2 at −79°: ○, base = py; △, base = pip; □, base = 1-Me(imid).

ner. Furthermore, the time required for complete formation of the carbon monoxide adduct increased as the injected volume of CO decreased, and was always longer than that required for complete formation of the oxygen adduct (eq 1). However, if the reaction was carried out in the presence of 1 atm of CO, the disappearance of Fe(TPP)$(py)_2$ was first order for greater than 90% of the reaction; under these conditions the value of $k^{f'}_{obsd}$ was found to be $(6.6 \pm 0.2) \times 10^{-3}$ sec^{-1} (average of three determinations). Within the limits of error, this value for $k^{f'}_{obsd}$ is identical with the corresponding value of k^{f}_{obsd} listed in Table I.

As described in the Experimental Section, the rate of oxygen displacement was studied by adding excess base to solutions containing Fe(TPP)(base)(O_2) under 1 atm of O_2.

$$\mathrm{Fe(TPP)(base)(O_2) + base \xrightarrow{k^{r}_{obsd}} Fe(TPP)(base)_2 + O_2} \quad (3)$$

For each of the base systems examined, the oxygen adduct disappeared in a first-order fashion (Figure 3). The observed rate constants are summarized in Table II. For the pyridine and 1-methylimidazole systems the amount of base added was sufficient to fully form Fe(TPP)$(base)_2$, and k^{r}_{obsd} was independent of added base concentration. The piperidine system will be considered in the Discussion Section.

An attempt was made to measure the rate at which carbon monoxide is displaced from Fe(TPP)(base)(CO).

$$\mathrm{Fe(TPP)(base)(CO) + base \xrightarrow{k^{r'}_{obsd}} Fe(TPP)(base)_2 + CO} \quad (4)$$

This reaction is extremely light sensitive. However, if appropriate light precautions are exercised, $k^{r'}_{obsd}$ for each of the complexes under study is too slow to be conveniently measured ($k^{r'}_{obsd} < 10^{-6}$ sec^{-1} at −79° in CH_2Cl_2).

An additional set of kinetic experiments examined the reaction between the oxygen adduct and carbon monoxide in methylene chloride at −79°.

$$\mathrm{Fe(TPP)(base)(O_2) + CO \xrightarrow{k^{e}_{obsd}} Fe(TPP)(base)(CO) + O_2} \quad (5)$$

The oxygen adduct was formed by adding 20-30 cm^3 of O_2 to Fe(TPP)$(base)_2$ (originally under 1 atm of N_2). The reaction was effected by adding a volume of CO equal to the amount of O_2 initially added (i.e., the resulting [CO] = [O_2] = $(3.8\text{-}5.7) \times 10^{-4}$ F). In all cases, the manner of disappearance of the oxygen adduct was first order. The observed rate constants are summarized in Table III.

Table II. Kinetic Data for the Reaction of Fe(TPP)(base)(O_2) and Excess Base in CH_2Cl_2 at −79°

Fe(TPP)(base)(O_2)[a]	Base	[base], F	k^{r}_{obsd},[b] sec^{-1}
Fe(TPP)(py)(O_2)	Pyridine	0.05	4.3×10^{-3}
		0.13	4.5×10^{-3}
		0.19	4.3×10^{-3}
		0.24	4.4×10^{-3}
Fe(TPP)(pip)(O_2)	Piperidine	0.41[c]	2.3×10^{-3}
		0.47[c]	2.5×10^{-3}
		0.59[c]	2.1×10^{-3}
Fe(TPP)(1-Me(imid))(O_2)	1-Methylimidazole	0.04	1.9×10^{-4}
		0.11	1.7×10^{-4}
		0.20	1.7×10^{-4}

[a] [Fe(TPP)(base)(O_2)] = $(2.6\text{–}6.6) \times 10^{-5}$ F; 1 atm of O_2. [b] Estimated error ±5%. [c] Range of piperidine concentrations limited by large [piperidine] required to displace oxygen from Fe(TPP)(pip)(O_2) (see Discussion Section).

Table III. Kinetic Data for the Reaction of Fe(TPP)(base)(O_2) with CO in CH_2Cl_2 at −79°[a]

Fe(TPP)(base)(O_2)[b]	k^{e}_{obsd}, sec^{-1}
Fe(TPP)(py)(O_2)	$(5.6 \pm 0.3) \times 10^{-4}$
Fe(TPP)(pip)(O_2)	$(5.1 \pm 0.5) \times 10^{-5}$
Fe(TPP)(1-Me(imid))(O_2)	$(5.4 \pm 0.4) \times 10^{-6}$

[a] Amount of CO added is equal to amount of O_2 initially injected (20–30 cm^3) to form the oxygen adduct. [b] [Fe(TPP)(base)(O_2)]$_0$ = $(1.3\text{–}6.0) \times 10^{-5}$ F.

Equilibrium Measurements. Equilibrium constants, K_{O_2}, were measured for the overall reaction:

$$\mathrm{Fe(TPP)(base)_2 + O_2 \overset{K_{O_2}}{\rightleftharpoons} Fe(TPP)(base)(O_2) + (base)} \quad (6)$$

where

$$K_{O_2} = \frac{[\mathrm{Fe(TPP)(base)(O_2)}][\mathrm{base}]}{[\mathrm{Fe(TPP)(base)_2}][\mathrm{O_2}]}$$

For each of the base systems, K_{O_2} was determined by adding known amounts of the specific base to a methylene chloride solution that originally contained only Fe(TPP)(base)(O_2) under 1 atm of O_2 at −79°. The resulting relative concentrations of oxygen adduct and bis(base) complex were determined spectrophotometrically. The oxygen dissolved in the equilibrium solution was known from the measurements described in the Experimental Section. Hence, it was possible to calculate K_{O_2}. The experiments were repeated with different quantities of added base, but the resulting amount of base was always 10^2-10^4 larger than the initial concentration of Fe(TPP)(base)(O_2). For the bases pyridine, piperidine, and 1-methylimidazole, the values for K_{O_2} were found to be 0.71 ± 0.05, 56.0 ± 8.0, and 5.4 ± 0.9, respectively (each value is the average of at least three independent determinations).

As a check on the above method, the equilibrium constant for the pyridine system was determined from the forward direction, i.e., by adding aliquots of air to a solution of Fe(TPP)$(py)_2$ containing no excess base. From spectral measurements, the concentrations of starting material and oxygen adduct in the equilibrium mixture could be calculated. The equilibrium concentration of free pyridine was assumed equal to that of the oxygen adduct. The oxygen concentration was found from the resulting partial pressure of O_2 above the solution and the oxygen solubility curve. For three separate aliquots of air (5, 10, and 20 cm^3), this approach gave a value of 1.03 ± 0.05 for K_{O_2}. This is in fairly good agreement with the value of 0.71 ± 0.05 found by the previously outlined procedure. The errors reported with each K_{O_2} reflect the *precision* of the experimental techniques. The value of 0.71 ± 0.05 is considered to be more *accurate* than the value of 1.03 ± 0.05. The former determination required knowing only the ratio $[Fe(TPP)(base)(O_2)]/[Fe(TPP)(base)_2]$, whereas the latter determination employed the actual concentrations of both species. Furthermore, the oxygen solubility under 1 atm of O_2 ("reverse" method) was known more accurately than the oxygen solubility at small partial pressures of O_2 ("forward" procedure). Therefore, comparing the accuracy attainable in each set of experiments, the value of 0.71 ± 0.05 is considered more reliable.

An attempt was made to determine the equilibrium constant which governs formation of the carbon monoxide adduct:

$$\mathrm{Fe(TPP)(base)_2} + \mathrm{CO} \overset{K_{CO}}{\rightleftharpoons} \mathrm{Fe(TPP)(base)(CO)} + \mathrm{base} \quad (7)$$

where

$$K_{CO} = \frac{[\mathrm{Fe(TPP)(base)(CO)}][\mathrm{base}]}{\mathrm{Fe(TPP)(base)_2}][\mathrm{CO}]}$$

However, K_{CO} proved too large to be measured by direct methods. As an alternative, an effort was made to find the partition constant, M, between oxygen and carbon monoxide in the reaction:

$$\mathrm{Fe(TPP)(base)(O_2)} + \mathrm{CO} \overset{M}{\rightleftharpoons} \mathrm{Fe(TPP)(base)(CO)} + \mathrm{O_2} \quad (8)$$

where

$$M = \frac{[\mathrm{Fe(TPP)(base)(CO)}][\mathrm{O_2}]}{[\mathrm{Fe(TPP)(base)(O_2)}][\mathrm{CO}]}$$

In these experiments a small aliquot of CO (4-40 cm^3) was added to a solution of $Fe(TPP)(base)(O_2)$ under 1 atm of O_2. Again, experimental limitations prevented the determination of an exact value for K_{CO} for any of the three complexes. However, lower limits for K_{CO} could be calculated and in all cases they were substantially larger than K_{O_2}. For the pyridine, piperidine, and 1-methylimidazole systems, the values of K_{CO} are larger than 2600, 750, and 160, respectively. The value for the piperidine system is consistent with Stynes and James[3] K_{CO} value for $Fe(TPP)(pip)_2$ of 1.5×10^4 at 23° in toluene.

Discussion

Under the experimental conditions outlined earlier (large excess of oxygen, no added base) the "forward" reactions of $Fe(TPP)(base)_2$ with O_2 to form the oxygen adduct proceed with a rate constant, k^f_{obsd}, that is independent of the oxygen concentration (see Table I). Such evidence is indicative of a dissociative mechanism in which the bis(base) species forms a five-coordinate intermediate, Fe(TPP)(base), prior to forming the six-coordinate product, $Fe(TPP)(base)(O_2)$.

Similarly, the "reverse" reactions of the six-coordinate oxygen adducts with excess base proceed with a rate constant, k^r_{obsd}, that is independent of the base concentration (see Table II). As above, this behavior suggests a dissociative mechanism in which the oxygen adduct forms a five-coordinate intermediate, Fe(TPP)(base), prior to forming the six-coordinate product, $Fe(TPP)(base)_2$.

Mechanism I is consistent with these observations:

$$\mathrm{Fe(TPP)(base)_2} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{Fe(TPP)(base)} + \mathrm{base}$$

$$\mathrm{Fe(TPP)(base)} + \mathrm{O_2} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \mathrm{Fe(TPP)(base)(O_2)}$$

For the reaction of the bis(base) species with oxygen, neglecting k_{-2} and assuming a steady state concentration of the five-coordinate species, mechanism I leads directly to the rate law:

$$\frac{-\mathrm{d}[\mathrm{Fe(TPP)(base)_2}]}{\mathrm{d}t} = \frac{k_1 k_2[\mathrm{Fe(TPP)(base)_2}][\mathrm{O_2}]}{k_{-1}[\mathrm{base}] + k_2[\mathrm{O_2}]}$$

If $k_2[O_2] \gg k_{-1}[base]$ then $-d[Fe(TPP)(base)_2]/dt = k_1[Fe(TPP)(base)_2]$ and $k_1 = k^f_{obsd}$ (see Table I).

For the reaction of the oxygen adduct with base to form the bis(base) species, assuming a steady state concentration of the five-coordinate species and neglecting k_1, the rate law is given by:

$$\frac{-\mathrm{d}[\mathrm{Fe(TPP)(base)(O_2)}]}{\mathrm{d}t} = \frac{k_{-1}k_{-2}[\mathrm{Fe(TPP)(base)(O_2)}][\mathrm{base}]}{k_{-1}[\mathrm{base}] + k_2[\mathrm{O_2}]}$$

If $k_{-1}[base] \gg k_2[O_2]$ then $-d[Fe(TPP)(base)[O_2)]/dt = k_{-2}[Fe(TPP)(base)(O_2)]$ and $k_{-2} = k^r_{obsd}$ (see Table II).

In the preceding derivations, assumptions were made concerning the relative values of $k_{-1}[base]$ and $k_2[O_2]$. For each of the base systems examined the value of k_2/k_{-1} is close to unity (see below). That is, k_2 and k_{-1} are not markedly different. For the "forward" reaction, the concentration of oxygen is much greater than that of base, justifying the assumption $k_2[O_2] \gg k_{-1}[base]$. For the "reverse" reaction, the concentration of base is greater than that of oxygen and again the assumption that $k_{-1}[base] \gg k_2[O_2]$ is justified.

Equilibrium constants for the reaction of oxygen with the bis(base) species, K_{O_2}, were measured as outlined earlier. It should be noted that K_{O_2} does not simply equal k^f_{obsd}/k^r_{obsd}, but, in terms of mechanism I,

$$K_{O_2} = \frac{k_1 k_2}{k_{-1}k_{-2}}$$

Having determined K_{O_2}, k_1, and k_{-2} for each of the base systems, the ratio (k_2/k_{-1}) can be calculated in each system (see Table IV). This ratio is a discrimination factor which gives the relative kinetic preference of the intermediate, Fe(TPP)(base), for oxygen vs. base.

In measuring k^r_{obsd} for the piperidine system, because of the large value of K_{O_2}, it was not feasible to add a sufficient amount of piperidine to completely form the bis(piperidine) complex. Therefore, in this system, k^r_{obsd} is not simply equal to k_{-2}. By combining the general expression for k^r_{obsd}, including the k_1 term, with the expression for K_{O_2} in terms of mechanm I, k_{-2} can be calculated:

$$k_{-2} = \frac{k_1 k^r_{obsd}[\mathrm{base}]}{k_1[\mathrm{base}] + k_1 K_{O_2}[\mathrm{O_2}] - k^r_{obsd}K_{O_2}[\mathrm{O_2}]}$$

Substitution of appropriate values into the above expression yields a value for k_{-2} of 1.5×10^{-3} sec^{-1}. This correction is not needed in the pyridine and 1-methylimidazole systems where, in measuring k^r_{obsd}, enough base was added to completely form the $Fe(TPP)(base)_2$ complex.

By analogy to the reaction with oxygen, the reaction of $Fe(TPP)(base)_2$ with carbon monoxide can be discussed in terms of mechanism II:

Table IV. Summary of Kinetic Parameters for Reaction of Fe(TPP)(base)$_2$ with O$_2$ and CO in Terms of Mechanisms I, II, and III[a]

Base	10^3k_1, sec^{-1}	10^3k_{-2}, sec^{-1}	K_{O_2}	k_2/k_{-1}[b]
Pyridine	6.6 ± 0.2	4.4 ± 0.1	0.71 ± 0.05	0.69 ± 0.06
Piperidine	28. ± 4.0	1.5 ± 0.1	56.0 ± 8.0	3.1 ± 1.2
1-Methyl-imidazole	0.61 ± 0.04	0.18 ± 0.01	5.4 ± 0.9	1.6 ± 0.5

Base	k_3/k_2	k_3/k_{-1}[c]	k_{-3},[d] sec^{-1}	K_{CO}
Pyridine	0.15 ± 0.01	0.10 ± 0.02	$<2 \times 10^{-7}$	>2600
Piperidine	0.035 ± 0.006	0.11 ± 0.06	$<4 \times 10^{-6}$	>750
1-Methyl-imidazole	0.031 ± 0.004	0.05 ± 0.02	$<2 \times 10^{-7}$	>160

[a] At −79° in CH$_2$Cl$_2$. [b] Calculated using $k_2/k_{-1} = K_{O_2}k_{-2}/k_1$. [c] Calculated using $k_3/k_{-1} = (k_2/k_{-1})(k_3/k_2)$. [d] Calculated using $k_{-3} = k_1k_3/k_{-1}K_{CO}$.

Table V. Comparisons between O$_2$ and CO Kinetic Parameters for Reactions with Heme Proteins at 20° (pH 7.0–7.4)

Heme	k_3/k_2	k_{-3}/k_{-2}	K_{CO}/K_{O_2}
Myoglobin[a] (horse)	0.016	1.08×10^{-3}	14.4
Myoglobin[b] (aplysia)	0.033	0.29×10^{-3}	114.0
Isolated α chains[c,d]	0.071	0.52×10^{-3}	133.0
Isolated β chains[c,d]	0.030	0.17×10^{-3}	180.0
Fe(TPP)(1-Me(imid))$_2$[e]	0.031	$<1.1 \times 10^{-3}$	>30.0

[a] G. A. Millikan, *Proc. R. Soc., London, Ser. B*, 120, 366 (1936). [b] B. A. Wittenberg, M. Brunori, E. Antonini, J. B. Wittenberg, and J. Wyman, *Arch. Biochem. Biophys.*, 111, 576 (1965). [c] M. Brunori, R. W. Noble, E. Antonini, and J. Wyman, *J. Biol. Chem.*, 241, 5238 (1966). [d] R. W. Noble, Q. H. Gibson, M. Brunori, E. Antonini, and J. Wyman, *ibid.*, 244, 3905 (1969). [e] This work at −79°, see also Table IV for corresponding values with pyridine and piperidine as axial bases.

$$\text{Fe(TPP)(base)}_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{Fe(TPP)(base)} + \text{base}$$

$$\text{Fe(TPP)(base)} + \text{CO} \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} \text{Fe(TPP)(base)(CO)}$$

For the reaction of the carbon monoxide adduct with base to form the bis(base) species, under the experimental conditions employed, $k^{r'}{}_{\text{obsd}}$ corresponds to k_{-3} (i.e., $k_{-3} < 10^{-6}$ sec^{-1} for each of the carbon monoxide adducts studied).

Again it should be noted that K_{CO}, the equilibrium constant for the reaction of carbon monoxide with Fe(TPP)(base)$_2$, is not equal to $k^{f'}{}_{\text{obsd}}/k^{r'}{}_{\text{obsd}}$, but in terms of mechanism II.

$$K_{CO} = \frac{k_1k_3}{k_{-1}k_{-3}}$$

The ratio k_3/k_{-1}, the relative preference of the five-coordinate intermediate for carbon monoxide vs. base can be calculated from the measured ratios k_3/k_2 (see below) and k_2/k_{-1}. These values, for each of the base systems, are tabulated in the summary of kinetic parameters presented in Table IV.

Consider the reaction between the oxygen adduct and carbon monoxide (eq 5) in terms of mechanism III:

$$\text{Fe(TPP)(base)(O}_2) \underset{k_2}{\overset{k_{-2}}{\rightleftharpoons}} \text{Fe(TPP)(base)} + \text{O}_2$$

$$\text{Fe(TPP)(base)} + \text{CO} \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} \text{Fe(TPP)(base)(CO)}$$

Under the experimental conditions described, the oxygen adduct disappeared in a first order fashion with a rate constant designated $k^{e}{}_{\text{obsd}}$. If the concentration of oxygen and the concentration of carbon monoxide are both much greater than that of the oxygen adduct, then mechanism III leads to the expression:

$$k^{e}{}_{\text{obsd}} = \frac{k_{-2}k_3[\text{CO}]}{k_2[\text{O}_2] + k_3[\text{CO}]}$$

However, the reaction was carried out with equal amounts of oxygen and carbon monoxide present. Then the above expression reduces to

$$k^{e}{}_{\text{obsd}} = \frac{k_{-2}k_3}{(k_2 + k_3)}$$

or rearranging

$$\frac{k_3}{k_2} = \frac{k^{e}{}_{\text{obsd}}}{(k_{-2} - k^{e}{}_{\text{obsd}})}$$

Using the values of k_{-2} (Table IV) and $k^{e}{}_{\text{obsd}}$ (Table III), k_3/k_2 can be calculated for each complex. The values for this ratio are given in Table IV. These results indicate that for each of the bases examined, the five-coordinate intermediate has a kinetic preference for oxygen over carbon monoxide. This conclusion is confirmed by two independent experimental observations. (1) When a solution of Fe(TTP)(base)$_2$ reacts with equal amounts of oxygen and carbon monoxide, the first adduct formed is that of oxygen; this species subsequently converts to the thermodynamically favored carbon monoxide adduct. (2) Large amounts of either O$_2$ or CO added to Fe(TPP)(base)$_2$ result in disappearance of the bis(base) complex at the dissociative limit (k_1). However, if smaller amounts of either gas are added, e.g., 20 cm^3, the oxygen addition still yields a $k^{f}{}_{\text{obsd}}$ equal to k_1, whereas the carbon monoxide addition results in a reaction rate substantially slower than the dissociative limit (i.e., $k_2[\text{O}_2]$ is still much greater than k_{-1}[base], but $k_3[\text{CO}]$ is no longer large enough to "swamp out" the k_{-1}[base] term).

The summary of the kinetic parameters in Table IV presents some interesting comparisons. The values of k_1 for the Fe(TPP)(base)$_2$ complexes show the same trend found by Stynes and James[3] for ferrous phthalocyanine complexes (i.e., pip > py > 1-Me(imid)). These authors have explained[3] this trend as reflecting the longer axial Fe-N bond in the piperidine complex compared to the imidazole species.

The values of k_{-2} are a measure of the lability of the coordinated oxygen in Fe(TPP)(base)(O$_2$). Unfortunately, these values cannot be quantitative compared with the values for the oxygenated heme proteins because of the large disparity in temperatures between measurements. However, the data in Table IV do reveal that k_{-2} is not simply a function of pK_a of the protonated axial base (pK_a(py) + 5.27,[16] pK_a(pip) 11.30,[16] and pK_a (1-Me(imid)) = 7.25).[17] When 1-methylimidazole is the axial base, the lability of O$_2$ is significantly less than that observed when piperidine or pyridine occupies the same position. This is particularly interesting if one considers that in the heme protein the axial ligand is an imidazole of the globin. As discussed in an earlier communication,[7] the lability of O$_2$ will be sensitive to the π-donor properties of the axial base. Hence the decreased lability of O$_2$ trans to 1-methylimidazole may reflect the better π-donor properties of this nitrogenous base. Enhanced oxygen binding to cobalt complexes with 1-methylimidazole in the trans position,[11,18] as well as enhanced CO binding to iron phthalocyanines with unsubstituted imidazole as the axial base,[3] have been attributed to the larger π-donor effect of imidazole relative to that of pyridine or piperidine. However, the relative order of lability in Fe(TTP)(pip)(O_2) vs. Fe(TPP)(py)(O_2) indicates that a strong σ-donor can overcome the effect of a moderate π-donor.

The equilibrium constants, K_{O_2}, reflect a number of different factors, including release of coordinated base, and cannot be simply compared. However, they do permit the calculation of k_2/k_{-1} which relates more directly to the biological system. The ratio k_2/k_{-1} is the relative tendency of the five-coordinate species to react with oxygen compared to reacting with the appropriate base. The values in Table IV indicate that in none of the base systems does the five-coordinate intermediate show an enormous perference for oxygen compared to the nitrogenous base. This illustrates the subtlety of the heme environment in the oxygen carrying proteins. At the active site of the protein, only one imidazole of the globin (the "proximal" imidazole) is close enough to covalently bind to the iron of the heme. The "distal" imidazole can stabilize the oxygen adduct through hydrogen bonding, but geometric constraints prevent its coordination to the iron center. The values of k_2/k_{-1} show that if the distal imidazole could bind to heme, it would seriously compete with oxygen for heme's available site (the local concentration of imidazole would be greater than that of oxygen), and the protein would cease to function as an effective oxygen carrier.[5]

In making comparisons between the kinetic parameters in Table IV and those which describe the binding of oxygen and carbon monoxide to myoglobin and hemoglobin, one must remember that reactons of Fe(TPP)(base)$_2$ involve a six-coordinate species whereas the active site of the protein is five coordinate. However, there are a number of comparisons which are not affected by this difference: k_3/k_2, k_{-3}/k_{-2}, and K_{CO}/K_{O_2}.

The ratio k_3/k_2 is a measure of the kinetic preference of the five-coordinate species for CO vs. O_2. Table V lists the value of this ratio for a number of heme proteins; these can be compared to the values for the model system listed in Table IV and repeated for Fe(TPP)(1-Me(imid)) in Table V. In both the model and the natural systems, the five-coordinate species reacts much faster with oxygen than with carbon monoxide. This may reflect more constraints in the transition state leading to the CO adduct compared to that leading to the O_2 adduct (the CO adduct is expected to be linear while the O_2 adduct is bent[19]). Consistent with this hypothesis, the reactions between myoglobin and either carbon monoxide or oxygen have similar enthalpies of activation, but the entropies of activation differ by a larger amount (myoglobin + CO, $\Delta H^\ddagger = 4.1$ kcal/mol, $\Delta S^\ddagger = -19.4$ eu; myoglobin + O_2, $\Delta H^\ddagger = 5.5$ kcal/mol, $\Delta S^\ddagger = -7.4$ eu[20]). However, the value of k_3/k_2 could also be due in part to the fact that O_2 is more electrophilic than CO and would be more capable of accommodating an odd electron. In terms of this supposition, triplet oxygen may be able to interact with Fe(TPP)(base), which is most likely high spin, through a more convenient pathway than is available to singlet carbon monoxide. Nitric oxide, which contains an unpaired electron, also reacts with heme proteins faster than carbon monoxide.[1]

In our kinetic studies we were able to determine only the upper limit of k_{-3} for Fe(TPP)(base)(CO). For each of the base systems examined, the value of k_{-3}/k_{-2} is less than 3×10^{-3} (Table IV). The deviation of this ratio from unity is in the same direction as exhibited by the natural systems and is consistent with the values listed in Table V.

The ratio of the equilibrium constants, K_{CO}/K_{O_2}, is not affected by [Fe(TPP)(base)$_2$] nor [base], since these terms divide out. For each of the base systems examined, K_{CO}/K_{O_2} is definitely greater than 13 (Table IV). Again, the deviation from unity is in the same direction as that exhibited by the heme proteins (Table V). In other words, the CO adducts of both the natural and model systems are considerably more thermodynamically favored than the O_2 adducts. For this reason, the synthetic iron complexes are better models for the natural oxygen carriers than are the cobalt chelates, which bind CO either very weakly[21] or not at all.[22]

Conclusions[23]

Simple tetraphenylporphyrinbis(base)iron(II) complexes reversibly bind oxygen at low temperatures. They display the same trends in reacting with oxygen and carbon monoxide as do the more complicated heme proteins, which suggests that the simple system is a satisfactory model for the active site of heme proteins. The intermediate Fe(TPP)(1-Me(imid)) reacts at about the same rate with 1-methylimidazole as it does with oxygen, indicating that heme proteins can function as oxygen carriers partly because the "distal" imidazole is structurally positioned such that it cannot coordinate to iron in competition with oxygen. Finally, the reactivity of these ferrous porphyrin complexes can be altered by varying the properties of the axial base.

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