

The Relationship Between Enthalpy Changes and Oxygenation Constants for Cobalt and Iron Porphyrins

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*The dioxygen uptake ability of $\text{Co}(\text{T}(\text{p-CH}_3\text{O})\text{-PP})\text{B}$, where $\text{T}(\text{p-CH}_3\text{O})\text{PP}$ is the dianion of 5,10,15,20-Tetra(*p*-methoxyphenyl)porphyrin and B is pyridine, piperidine, and N-methylimidazole, was studied in toluene and methylene chloride. A general trend between $\log K_{\text{O}_2}$ (standard state of 1 Torr) and ΔH_{O_2} was found for cobalt synthetic complexes, cobalt 'natural' complexes, and iron 'natural' complexes. The linear relationships have similar slopes, similar temperature dependences, but different intercepts. The difference in intercepts is attributed to differences in entropies arising from solvation effects. When the latter linear relationship is coupled with the near linear dependence of ΔH for precursor complex formation, $\text{Co}(\text{T}(\text{p-CH}_3\text{O})\text{PP}) + \text{B} \rightleftharpoons \text{Co}(\text{T}(\text{p-CH}_3\text{O})\text{-PP})\text{B}$, and ΔH_{O_2} , a powerful predictive tool arises for the estimation of the oxygen uptake ability of the complex from the enthalpy change of the precursor formation reaction.*

Introduction

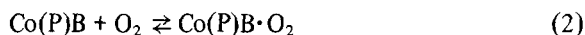
A large number of cobalt porphyrin complexes have been studied as model systems for hemoglobin and myoglobin [1, 2]. These complexes are related to dioxygen carrying hemoproteins by the fact that they generally form a five coordinate precursor complex with amine bases in nonaqueous solvents and can reversibly form 1:1 adducts with molecular oxygen. In an effort to link iron and cobalt systems, Hoffman and Petering [3] prepared the cobalt analogue of myoglobin called coboglobin. The authors concluded that the dioxygen binding constant for coboglobin was ~300 times greater than for the imidazole adduct of the cobalt porphyrin complex in solution [4]. The greater enhancement of dioxygen binding in horse coboglobin was report-

ed to be entirely entropic; that of whale coboglobin was both enthalpic and entropic.

Since that time a large number of studies have been published including work with 'picket fence' [5] and 'capped' [6, 7] porphyrin complexes. It has also been demonstrated that a correlation exists between the enthalpy of precursor formation of the five coordinate intermediate $\text{Co}(\text{P})\text{B}$ in equation 1, where P is a porphyrin ligand and B an axial base,



and the enthalpy of the dioxygen uptake reaction given in equation 2 [8].



The accumulated evidence can now be combined and a more general picture emerges.

The system that we studied involved dioxygen uptake by $\text{Co}(\text{T}(\text{p-CH}_3\text{O})\text{PP})\text{B}$, where $\text{T}(\text{p-CH}_3\text{O})\text{-PP}$ is the dianion of 5,10,15,20-Tetra(*p*-methoxyphenyl)porphyrin and B represents pyridine (py), piperidine (pip), and N-methylimidazole (N-Melm), in methylene chloride and toluene. Formation constants for $\text{Co}(\text{T}(\text{p-CH}_3\text{O})\text{PP})\text{B}$ have been published elsewhere [9].

Experimental

Preparation of the complex and purification and drying of the solvents has been previously discussed [9]. Absorption spectral changes used for determining equilibrium constants were recorded on a Cary 14 Recording Spectrophotometer. A low temperature pyrex cell designed so that a slush bath could completely surround the solution in the light path (5.2 cm) without interfering with the light beam was used in the measurements [10]. Liquids were used for slushes as described by Shriver [11]

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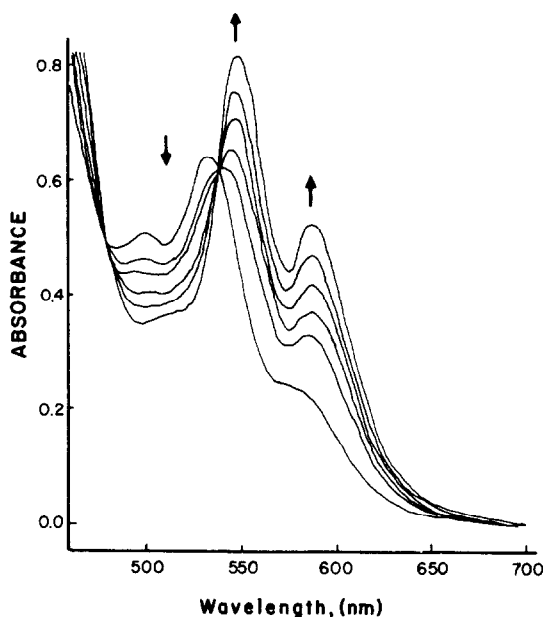


Fig. 1. Spectral changes of $\text{Co}(\text{T}(\text{p-CH}_3\text{O})\text{PP})(\text{pip})$ in methylene chloride at -33.6°C as the oxygen pressure was increased over the solution.

and include carbon tetrachloride (-23.4°C), anisole (-36.8°C), 3-pentanone (-41.4°C), chlorobenzene (-45.0°C), ethylmalonate (-49.0°C), benzaldehyde (-54.0°C), mesityl oxide (-59.0°C), and chloroform (-63.5°C). Solution temperatures were determined using a Honeywell Potentiometer and an iron-constantan thermocouple referenced against 0°C .

Equilibrium Constant Measurements

A solution of $\text{Co}(\text{T}(\text{p-CH}_3\text{O})\text{PP})$ was prepared under nitrogen and the concentration was adjusted by dilution techniques until it had an absorbance from 0.75 to 0.85 in the titration cell. The concentration was approximately $1 \times 10^{-5} \text{ M}$ under the conditions. A 25 ml aliquot of solution was then added by pipet to the low temperature cell which had previously been flushed with nitrogen. The cell was evacuated and the solution was degassed by boiling off a small amount ($<2\%$) of the solvent to assure that no dioxygen had inadvertently been dissolved in the solution or had entered the titration vessel. The amount of base needed to form 99.9% of the base adduct at the desired temperature was then added. The concentration needed for this was first calculated from the thermodynamic parameters obtained from the base addition reactions [9].

After the titration solution was completely prepared, the cell was then evacuated; and the cryostatic bath of the required temperature was added. The solution was allowed to stand about twenty minutes to come to thermal equilibrium, and the cell was

then mounted in the cell compartment of the Cary 14. A spectrum was then recorded between 700 nm and 450 nm. Next the cell was connected to a vacuum manifold, which had both a closed end manometer and a source of dioxygen attached. The vapor pressure of the solution was first measured, and the titration with dioxygen was started.

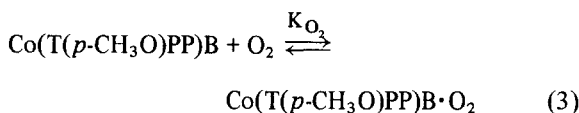
The titration was carried out by increasing the pressure of dioxygen in the cell and the manifold stepwise from 0 to about 830 Torr. The observed vapor pressure of the solution was subtracted from each pressure reading. After each dioxygen addition, the cell was shaken vigorously to stir the solution and to insure that the maximum amount of dioxygen had been dissolved. The required mixing time for each system was determined by adding a small amount of dioxygen and repetitively shaking the cell and recording the spectrum until two successive spectra reproduced each other.

The reversibility of the oxygenation reaction in a given solvent and base combination was verified by evacuating the cell at the end of the titration and recording a spectrum after several seconds of shaking. If the spectrum so obtained reproduced the original spectrum, the reaction was considered to be reversible in that solvent.

Results

Dioxygen Uptake

Figure 1 illustrates the spectral changes observed as the pressure of dioxygen was increased over a solution of $\text{Co}(\text{T}(\text{p-CH}_3\text{O})\text{PP})\text{B}$, where B is pyridine, or piperidine, or N-methylimidazole. As the dioxygen pressure increased, the band at 532 nm decreased in absorbance and was replaced by two bands at approximately 550 nm and 590 nm which were characteristic of the dioxygen adduct. Two isosbestic points were observed at 513 and 533 nm. The actual positions of these peaks and isosbestic points varied slightly from solvent to solvent, and from base adduct to base adduct. The equilibrium constants of formation of the dioxygen adduct (equation 3) were determined from the increase in absorbance of the bands at 550 and 590 nm and were



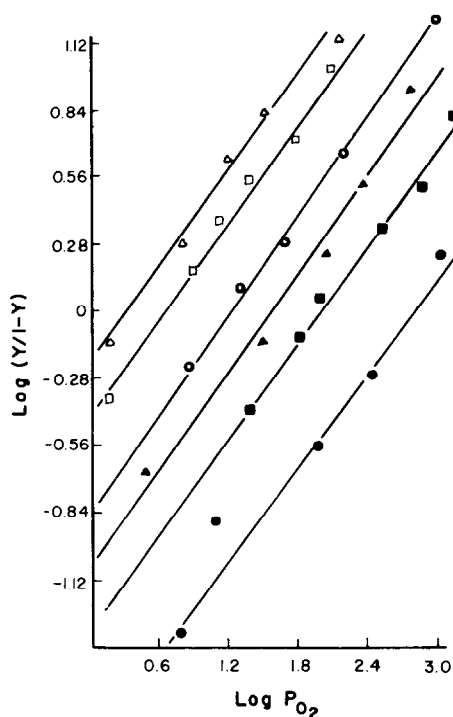
collected in the temperature range of -20°C to -60°C .

The equilibrium constants were obtained using the Hill equation [12] where Y

$$\log(Y/1 - Y) = n \log P_{\text{O}_2} + \log K_{\text{O}_2} \quad (4)$$

TABLE I. Equilibrium Constants for the Reaction of Co(T(*p*-CH₃O)PP)B with Dioxygen in Methylene Chloride and Toluene.

Solvent	Co(T(<i>p</i> -CH ₃ O)PP)py		Co(T(<i>p</i> -CH ₃ O)PP)pip		Co(T(<i>p</i> -CH ₃ O)PP)N-MeIm	
	T (°C) ^a	LogK _{O₂} ^b	T (°C) ^a	LogK _{O₂} ^b	T (°C) ^a	LogK _{O₂} ^b
Methylene Chloride	-30.8	-2.50	-30.8	-1.86	-17.6	-1.81
	-34.8	-2.34	-41.8	-1.30	-23.4	-1.57
	-36.8	-2.18	-45.3	-1.01	-30.6	-1.25
	-45.0	-1.84	-48.3	-0.78	-37.4	-0.97
	-50.8	-1.55	-48.8	-0.79	-41.8	-0.65
	-54.5	-1.31	-49.0	-0.79	-44.8	-0.46
			-57.2	-0.38		
			-60.4	-0.17		
			-60.6	-0.16		
Toluene	-49.0	-2.96	-39.2	-3.34	-50.6	-1.81
	-50.6	-2.91	-45.3	-3.06	-56.8	-1.52
	-55.8	-2.69	-50.6	-2.91	-59.6	-1.38
	-58.8	-2.57	-60.6	-2.43	-63.8	-1.18
	-63.5	-2.31	-62.8	-2.25	-65.0	-1.07
			-62.8	-2.31		

^a ± 0.01 °C. ^b ± 0.02 Standard State of 1 Torr.Fig. 2. Plot of $\log(Y/(1-Y))$ vs. $\log P_{O_2}$ for Co(T(*p*-CH₃O)PP)(pip) in methylene chloride at several temperatures. Δ -60.4; \square -57.2; \circ -48.8; \blacktriangle -45.3; \blacksquare -41.8; \bullet -30.8.

equals the total fraction of metal porphyrin binding dioxygen. Least squares analyses determined on the data from systems in which oxygenation was nearly complete showed that the slopes in plots of \log

$(Y/(1-Y))$ vs. $\log P_{O_2}$ were very close to one. Normally, oxygenation was not complete. In order to calculate formation constants for the latter systems, a modified least squares analysis program was used which adjusted the slope of the line to one by successive approximations. Log K_{O₂} values were thus obtained from the intercepts. Figure 2 shows some typical examples of straight lines of slopes constrained to one for plots of $\log[Y/(1-Y)]$ vs. $\log P_{O_2}$. The very small deviations of the data points from the least squares lines justified the assumption that the reaction between the base adduct and oxygen always occurred in a 1:1 ratio. Table I contains the equilibrium constants determined at their corresponding temperatures.

Equation 5, as given by Drago [13], was also used to spot-check calculations of the equilibrium con-

$$K^{-1} = P_{O_2} \left[\frac{[BCoP]_A b (\epsilon_A - \epsilon_C)}{A_o - A} - 1 \right] \quad (5)$$

stants determined above. The variables in the equation are as follows: *b* is the optical cell path length, ϵ_A is the absorption coefficient of Co(T(*p*-CH₃O)PP)B, ϵ_C is the absorption coefficient of Co(T(*p*-CHO)PP)B·O₂, [BCoP]_A is the initial concentration and *A*_o is the initial absorbance of Co(T(*p*-CH₃O)PP)B, and *A* is the absorbance of the solution at the pressure of oxygen, *P*_{O₂}. Equation (5) was modified to (6) and fitted to a least squares analysis. The equilibrium constants *K* obtained from equation (6)

$$\left[\frac{[BCoP]_A b (\epsilon_A - \epsilon_C)}{A_o - A} - 1 \right]^{-1} = P_{O_2} K \quad (6)$$

TABLE II. Thermodynamic Parameters for the Reaction of $\text{Co}(\text{T}(\text{p-CH}_3\text{O})\text{PP})\text{B}$ with Dioxygen in Methylene Chloride and Toluene.

Compound	Methylene Chloride			Toluene		
	$\text{Log } K_{\text{O}_2}, \text{ mm}^{-1} \text{ a}$	$\Delta H_{\text{O}_2}, \text{ kcal/mol}^b$	$\Delta S_{\text{O}_2}, \text{ e.u.}^b$	$\text{Log } K_{\text{O}_2}, \text{ mm}^{-1} \text{ a}$	$\Delta H_{\text{O}_2}, \text{ kcal/mol}^b$	$\Delta S_{\text{O}_2}, \text{ e.u.}^b$
$\text{Co}(\text{T}(\text{p-CH}_3\text{O})\text{PP})\text{py}$	-1.68	-11.9(0.3)	-61(1)	-2.84	-9.6(0.4)	-56(2)
$\text{Co}(\text{T}(\text{p-CH}_3\text{O})\text{PP})\text{pip}$	-0.86	-13.4(0.7)	-64(3)	-2.88	-10.0(0.3)	-58(2)
$\text{Co}(\text{T}(\text{p-CH}_3\text{O})\text{PP})(\text{N-Melm})$	-0.15	-13.0(0.5)	-59(2)	-1.83	-10.4(0.5)	-55(2)

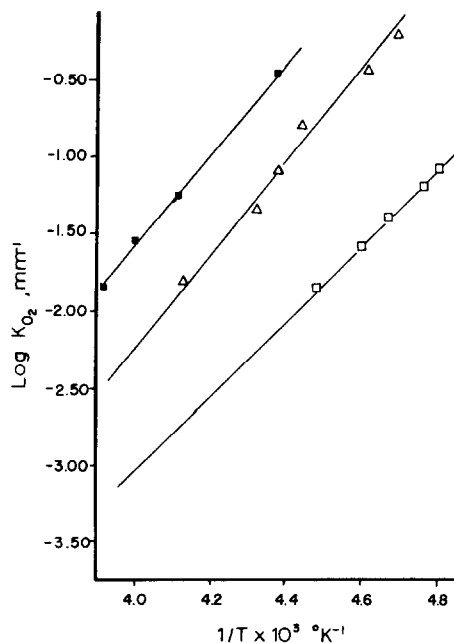
^aCalculated from ΔH_{O_2} and ΔS_{O_2} values at -50°C . Standard State of 1 Torr.^bError in parenthesis; at 90% confidence level.

Fig. 3. Van't Hoff plots for enthalpy and entropy change determinations for the formation of oxygen adducts in several solvent base combinations. ■ Methylene Chloride/N-Melm; △ Methylene Chloride/piperidine; □ Toluene/N-Melm.

were similar to the ones calculated from the Hill equation verifying the fact as pointed out by others [14] that the above calculations reduce to the Hill equation under the conditions where the concentration of ligand is much greater than the complex. In this case, $[\text{O}_2] \sim 10^{-2} M \gg [\text{BCoP}] \sim 10^{-5} M$.

The enthalpy and entropy parameters for the dioxygen titration results were derived from van't Hoff plots of $\log K_{\text{O}_2}$ vs. $1/T$ as illustrated in Fig. 3. The data, including errors as derived from the linear least squares regression analysis, are given in Table II.

Discussion

The Thermodynamics of Dioxygen Uptake

The three axial base complexes, $\text{Co}(\text{T}(\text{p-CH}_3\text{O})\text{PP})\text{B}$, where B = pyridine, piperidine, and N-methylimidazole, were chosen for this study. Previous studies indicated that the order of increased dioxygen uptake for the change in axial ligation was in the order of $\text{py} < \text{pip} < \text{N-Melm}$ for cobalt Schiff-base complexes [1]. This ordering was found even though the σ and π -bonding properties of these ligands varied.

The change in solvent does have a pronounced effect on the reversible oxygenations of cobalt complexes. The $\text{Co}(\text{PP}(\text{IX})\text{DME})(\text{N-Melm})$ complex formed a 33 times more stable dioxygen adduct in DMF than in toluene at -23°C [15]. The effect

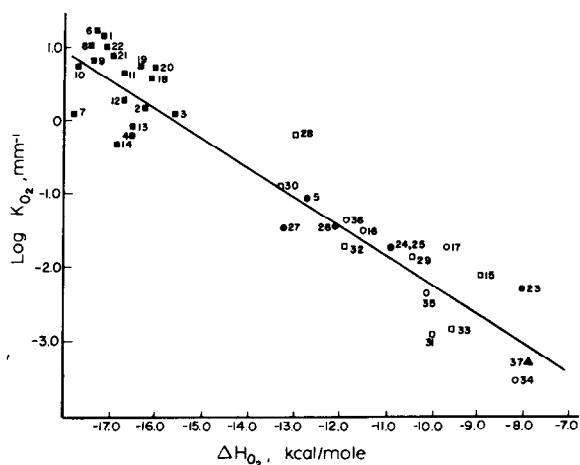


Fig. 4. Dependence of the dioxygen adduct formation constant ($\log K_{O_2}$) at -50°C for a large number of synthetic cobalt complexes with the enthalpy change for the process.

(complex)(axial base)/solvent	(calculated from)
1, Co(acacen)(py)/toluene	(ref. 17)
2, Co(Phacacen)(py)/toluene	(ref. 17)
3, Co(Meacacen)(py)/toluene	(ref. 17)
4, Co(Benacen)(py)/toluene	(ref. 17)
5, Co(Sacsacen)(py)/toluene	(ref. 17)
6, Co(Benacen)(<i>n</i> -butylamine)/toluene	(ref. 17)
7, Co(Benacen)(<i>iso</i> -butylamine)/toluene	(ref. 17)
8, Co(Benacen)(<i>N</i> -MeIm)/toluene	(ref. 17)
9, Co(Benacen)(5-Cl- <i>N</i> -MeIm)/toluene	(ref. 17)
10, Co(Benacen)(<i>sec</i> -butylamine)/toluene	(ref. 17)
11, Co(Benacen)(pip)/toluene	(ref. 17)
12, Co(Benacen)(3,4-lutidine)/toluene	(ref. 17)
13, Co(Benacen)(py)/toluene	(ref. 17)
14, Co(Benacen)(CN-py)/toluene	(ref. 17)
15, Co(T(<i>p</i> -CH ₃ O)PP)(py)/toluene	(ref. 21)
16, Co(PIXDME)(<i>N</i> -MeIm)/toluene	(ref. 18)
17, Co(PIXDME)(<i>N</i> -MeIm)/toluene	(ref. 8)
18, Co(Benacen)(py)/toluene	(ref. 20)
19, Co(CH ₃ OBenacen)(py)/toluene	(ref. 20)
20, Co(CH ₃ Benacen)(py)/toluene	(ref. 20)
21, Co(BrBenacen)(py)/toluene	(ref. 20)
22, Co(ClBenacen)(py)/toluene	(ref. 20)
23, Co(Bensacen)(py)/toluene	(ref. 20)
24, Co(CH ₃ OBensacen)(py)/toluene	(ref. 20)
25, Co(CH ₃ Bensacen)(py)/toluene	(ref. 20)
26, Co(BrBensacen)(py)/toluene	(ref. 20)
27, Co(ClBensacen)(py)/toluene	(ref. 20)
28, Co(T(<i>p</i> -CH ₃ O)PP)(<i>N</i> -MeIm)/methylene chloride	(this work)
29, Co(T(<i>p</i> -CH ₃ O)PP)(<i>N</i> -MeIm)/toluene	(this work)
30, Co(T(<i>p</i> -CH ₃ O)PP)(pip)/methylene chloride	(this work)
31, Co(T(<i>p</i> -CH ₃ O)PP)(pip)/toluene	(this work)
32, Co(T(<i>p</i> -CH ₃ O)PP)(py)/methylene chloride	(this work)
33, Co(T(<i>p</i> -CH ₃ O)PP)(py)/toluene	(this work)
34, Co(MPIXDME)(S(CH ₃) ₂)/toluene	(ref. 19)
35, Co(MPIXDME)(P(OCH ₃) ₂)/toluene	(ref. 19)
36, Co(MPIXDME)(P(C ₄ H ₉) ₃)/toluene	(ref. 19)
37, Co(Cap)(<i>N</i> -MeIm)/toluene	(ref. 7).
■ acacen derivatives; □ T(<i>p</i> -CH ₃ O)PP; ● sacacen derivative; ○ PIXDME and MPIXDME; ▲ cap.	

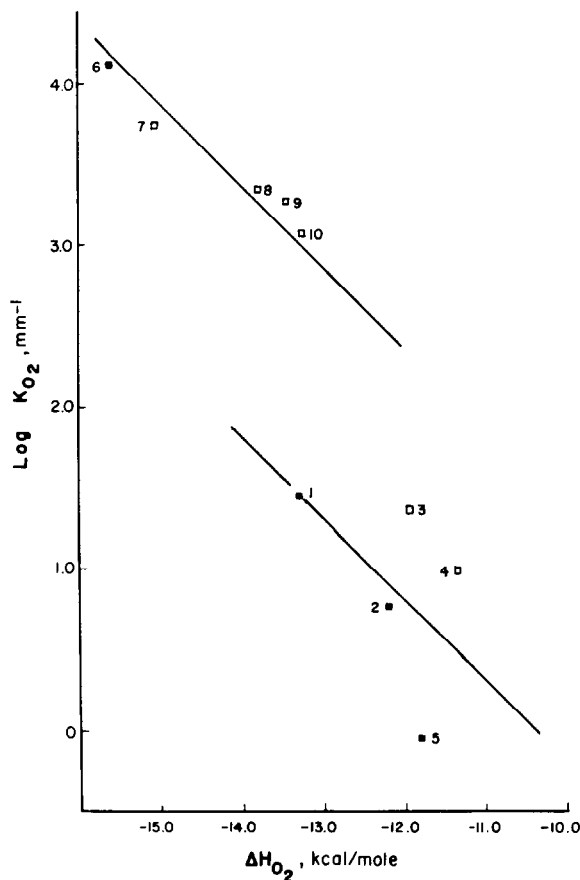


Fig. 5. Dependence of the dioxygen adduct formation constant ($\log K_{O_2}$) at -50°C for a number of 'natural' cobalt and iron complexes with the enthalpy change for the process.

(complex)(axial base)/solvent	(calculated from)
1, Co(TpivPP)(<i>N</i> -MeIm)/solid	(ref. 22)
2, Co(TpivPP)(<i>N</i> -MeIm)/toluene	(ref. 22)
3, Co(Mb)(Whale)/pH7	(ref. 3,4)
4, Co(Mb)(Horse)/pH7	(ref. 3,4)
5, Co(TpivPP)(1,2-DiMeIm)/toluene	(ref. 22)
6, Fe(TpivPP)(<i>N</i> -MeIm)/solid	(ref. 24)
7, Ox Myoglobin (Adult)	(ref. 26)
8, Horse Myoglobin	(ref. 25)
9, Human Myoglobin	(ref. 25)
10, Tuna Myoglobin	(ref. 27).
■ 'synthetic' ligands □ 'natural' ligands	

is even greater for the Co(T(*p*-CH₃O)PP)B complexes studied here (Table II). There is over two orders of magnitude (~ 105) difference in K_{O_2} for reactions of Co(T(*p*-CH₃O)PP)(pip) with dioxygen in methylene chloride compared to toluene at -50°C .

The difference in dioxygen uptake of the cobalt porphyrin complexes in this study is closely associated with the enthalpy change for the process. Plots of $\log K_{O_2}$ at -50°C vs. ΔH_{O_2} are linear with data points symmetrically distributed about a line through the center. The apparent correlation between

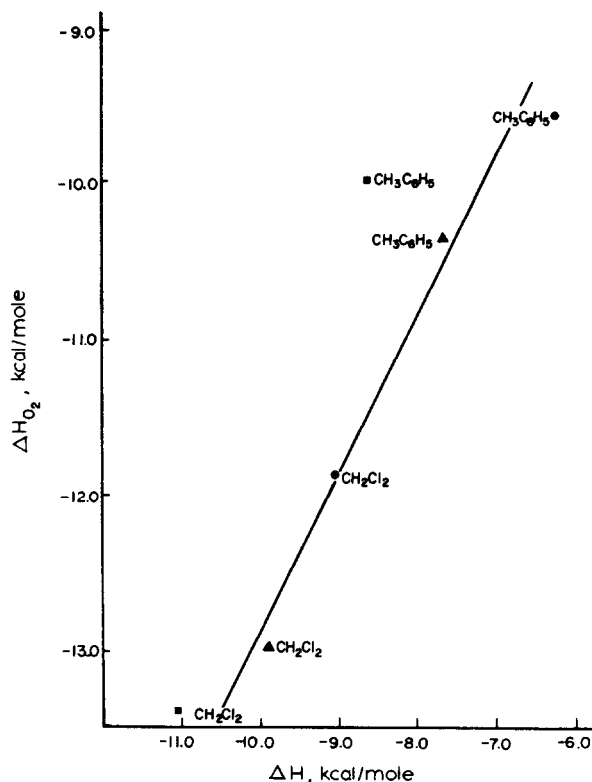


Fig. 6. Variation of the enthalpy change (ΔH_{O_2}) for the dioxygen addition reaction of $\text{Co}(\text{T}(\text{p-CH}_3\text{O})\text{PP})\text{B}$ with the enthalpy change (ΔH) for the formation of the precursor complex. \bullet $\text{Co}(\text{T}(\text{p-CH}_3\text{O})\text{PP})(\text{py})$; \blacksquare $\text{Co}(\text{T}(\text{p-CH}_3\text{O})\text{PP})(\text{pip})$; \blacktriangle $\text{Co}(\text{T}(\text{p-CH}_3\text{O})\text{PP})(\text{N-Melm})$.

ΔH_{O_2} and the ease of dioxygen uptake by cobalt complexes was previously pointed out by Tazher, *et al.* [16]. Accompanying the change in ΔH_{O_2} is a change in ΔS_{O_2} in the same direction. This change in ΔS_{O_2} , however, does not seem to effect the general correlation observed in plots of $\log K_{O_2}$ vs. ΔH_{O_2} .

Addition of data available in the literature for cobalt synthetic dioxygen carriers [7, 8, 17–21] results in the plot shown in Fig. 4. The slope of the least squares lines is -0.40 ± 0.02 . The linear relationship between $\log K_{O_2}$ and ΔH_{O_2} from literature data on a cobalt 'picket' fence porphyrin [22] and several dioxygen carriers reconstituted with a cobalt porphyrin complex [3, 4, 23] is illustrated in Fig. 5. Even more interesting is the extension of this procedure to iron 'picket' fence [24] and natural [25–27] systems. The linear relationship illustrated in Fig. 5. was observed in this case also. The slope of the least squares line is -0.39 ± 0.04 , which is nearly identical to the dependence observed in Fig. 4. This line is displaced from that of the

analogous cobalt complexes, reflecting the greater sensitivity of the iron systems to dioxygenation.

The linear relationships imply that the equilibrium constants at -50°C could readily be determined from an equation of the form

$$\log K_{O_2} = -0.4 \Delta H_{O_2} + c \quad (7)$$

where ΔH_{O_2} is in kcal/mol and c represents the intercept of the respective $\log K_{O_2}$ vs. ΔH_{O_2} plots.

Equation 7 can be generalized by determining the functional temperature dependence of the slopes* for the systems in Figs. 4 and 5, and substituting the corresponding values of c . These steps lead to the following equations which indicate that the relationship between $\log K_{O_2}$ and ΔH_{O_2} is similar in each system.

$$\text{cobalt-synthetic} \quad \log K_{O_2} = \left(-\frac{218}{T} + 0.59 \right) \Delta H_{O_2} - 6.20 \quad (8)$$

$$\text{cobalt-'natural'} \quad \log K_{O_2} = \left(-\frac{218}{T} + 0.59 \right) \Delta H_{O_2} - 3.53 \quad (9)$$

$$\text{iron-'natural'} \quad \log K_{O_2} = \left(-\frac{218}{T} + 0.59 \right) \Delta H_{O_2} - 2.03 \quad (10)$$

The primary difference among the three systems is reflected in the constant 'c'. There is a pronounced parallel between the differences in the average entropy change for each series and the differences between the values of 'c'. The parallel implies that the ability of a complex to carry dioxygen depends in part on the extent to which solvent molecules must orient themselves in order to stabilize the charge

separated product, $\text{Co}^{\delta+}-\text{O}^{\delta-}$. The greater solvent orientation observed in cobalt synthetic systems results in the decreased oxygen sensitivity. The molecular basis for the more favorable entropy change for binding of dioxygen in the protein environment has been discussed by Hoffman and co-workers [3, 4]. They suggested that the 'pocket' of globin is organized prior to the binding of dioxygen and this negative entropy is associated with formation of the precursor complex, not as a contribution to the entropy change upon binding of dioxygen.

Although this may account for the major difference, observed entropy changes for dioxygen binding also reflect several contributions which include a decrease of ~ 25 e.u. due to a loss of dioxygen trans-

*For systems in Figs. 4 and 5, slopes of $\log K_{O_2}$ vs. ΔH_{O_2} plots determined at various temperatures were plotted as a function of $1/T$. These plots were linear and each had a slope of $-218/T$ and an intercept of 0.59.

TABLE III. Comparison of LogK_{O_2} Values Determined Theoretically from Thermodynamics and Empirically Using Equations 8–10 to the Values Determined Experimentally.

Compound/Solvent	t °C	LogK_{O_2} (exp) ^a	LogK_{O_2} (theo) ^a	LogK_{O_2} (emp) ^a	Ref.
Co(Meacacen)(py)/CH ₃ C ₆ H ₅ ^b	–31	–1.12	–1.12	–1.21	17
Co(T(<i>p</i> -CH ₃ O)PP)(pip)/CH ₂ Cl ₂	–57	–0.38	–0.43	–0.43	This work
Co(TpivPP)(N-MeIm)/CH ₃ C ₆ H ₅ ^c	25	–2.15	–2.26	–2.04	21
CoMb(Whale)/pH = 7	25	–1.76	–1.85	–1.91	3, 4
Fe(TpivPP)(N-MeIm)/solid ^c	20	0.51	0.44	0.36	23

^aStandard state of 1 Torr, units mm^{-1} . ^bCo(Meacacen), N,N'-ethylenebis(3-methylacetylacetoniminato)cobalt(II). ^c(TpivPP), Dianion of *meso*-Tetra ($\alpha,\alpha,\alpha,\alpha$ -o-pivalamidophenyl)porphyrin.

TABLE IV. Comparison of $\log K_{\text{O}_2}$ Values Determined Experimentally to Those Derived from Equation 8 After Substitution of the Dependence of ΔH_{O_2} on ΔH for Precursor Formation of Cobalt Porphyrin Complexes in Toluene and Methylene Chloride.

Complex	t °C	ΔH , kcal/mol	LogK_{O_2} (exp) ^a , mm^{-1}	LogK_{O_2} (calc) ^a , mm^{-1}	Reference
Co(T(<i>p</i> -CH ₃ O)PP)py ^b	–50.6	–6.2 ^d	–2.91	–2.62	This work
Co(T(<i>p</i> -CH ₃ O)PP)N-MeIm ^b	–50.6	–7.6 ^d	–1.81	–2.16	This work
Co(PPIXDME)N-MeIm ^b	–31	–10.7	–2.36	–2.15	18
Co(PPIXDME)py ^b	–57.5	–6.9	–2.25	–2.09	18
Co(PPIXDME)P(OCH ₃) ₃ ^b	–66.0	–6.9	–1.55	–1.68	19
Co(T(<i>p</i> -CH ₃ O)PP)py ^c	–45.0	–9.0 ^d	–1.84	–1.93	This work
Co(T(<i>p</i> -CH ₃ O)PP)pip ^c	–45.3	–11.1 ^d	–1.01	–1.11	This work

^aStandard state of 1 Torr. ^bIn toluene. ^cIn methylene chloride. ^dReference 9.

lational entropy and partial loss of ligand rotational entropy, an increase from displaced solvent from dioxygen and the metalloporphyrin precursor complex, and a decrease for solvation of the metalloporphyrin dioxygen complex. It is found that the precursor complexes which give rise to the most negative enthalpy and entropy changes upon formation also give rise to the most negative thermodynamic values upon oxygenation. This means that greater entropy change associated with desolvation of the precursor complex must be more than compensated for by resolution of the dioxygen adduct, provided the other entropy contributors remain nearly constant.

The metal center causes the primary difference between the oxygen sensitivity of iron and cobalt natural systems. The primary difference in dioxygen sensitivity resides in the greater enthalpy of iron–dioxygen adduct formation, but this is also accompanied by a smaller entropy factor. The iron systems apparently form stronger metal–dioxygen bonds and also require less solvent orientation than their cobalt analogues [28–31].

This is supported by literature data. The metal–dioxygen bond distance for a dioxygen adduct of

a cobalt Schiff-base complex was reported to be 1.86 Å [29] whereas that of an iron 'picket' fence porphyrin was 1.75 Å [28]. This difference between the Co(II)–O–O and Fe(II)–O–O bond length has been used to suggest possible multiple bonding for the latter case. Although the Fe(II)–O–O bond has been suggested to be dipolar to account for the dioxygen uptake solvent dependence [32], theoretical calculations indicate that charge separated Fe(III)–O₂[–] is not favorable, whereas for the analogous Co(II)–O–O complex a net charge varying from 0.1 to 0.8e is transferred from the cobalt center to the dioxygen ligand. This charge delocalization (or lack of it) would account for the difference in solvation entropies between the iron and cobalt natural dioxygen carriers.

A comparison of $\log K_{\text{O}_2}$ values determined in three ways is presented in Table III. The experimental values are compared to those determined from ΔH_{O_2} and ΔS_{O_2} values and from equations 8–10. Errorwise, the empirical and thermodynamic calculated dioxygen uptake constants are not too different from the experimental ones.

Another powerful prediction tool can be presented based on the fact reported by Drago, *et al.* where a

linear relationship was observed between ΔH of precursor formation and ΔH_{O_2} found for reversible dioxygenations of cobalt porphyrin complexes [8]. A plot of this type is shown in Fig. 6. A general trend is observed with $\Delta H_{O_2} = 0.9\Delta H - 4$. Substitution of this equation into equation 8 allows the prediction of $\log K_{O_2}$ from more easily obtained ΔH values. In Table IV, some experimental values are compared to those obtained using the modified equation. The calculated result give estimates within the 90% confidence level of those found experimentally.

Conclusion

The modeling approach for understanding the behavior of hemoglobin and myoglobin through studies of dioxygen uptake by cobalt porphyrin complexes is a useful one. Estimates of $\log K_{O_2}$ for cobalt and iron complexes in a 'natural' environment can be made using Figs. 4 and 5. A vertical displacement from the ΔH_{O_2} value of the cobalt synthetic compound in Fig. 4 to the line of the cobalt 'natural' systems in Fig. 5 will lead to the value of $\log K_{O_2}$ at -50°C for the cobalt complex in a protein environment*. The procedure in going from cobalt complexes to iron systems requires a vertical displacement and a 2 to 4 kcal/mol shift to the left**. The vertical displacement in the case of comparing cobalt synthetic to cobalt 'natural' systems suggests that the nature of the cobalt-oxygen bond remains the same in both environments. ESR evidence has indicated that indeed the electronic and geometric structure of the cobalt adduct in both environments is similar [3]. The vertical displacement and shift to the left in going to iron complexes indicates that the nature of the iron-oxygen bond is different than that of the cobalt oxygen one. As pointed out above, partial double bond character has been suggested for Fe-O-O and this would account for the more negative enthalpy change.

Values of $\log K_{O_2}$ at other temperatures can be obtained using equations 8-10. For purposes of calculations, enthalpy changes for cobalt systems can be assumed to be similar whereas iron 'natural' compounds can be assumed to be 2 to 4 kcal/mol more

negative. Thus, knowledge of ΔH_{O_2} in one system will allow calculation of oxygenation constants in the other system at the desired temperature.

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*For example, compare ΔH_{O_2} for Co(PPIXDME)-(N-MeIm) (-11.5 kcal/mol) to horse coboglobin (-11.5 kcal/mol) [4].

**It is estimated on the basis of the accumulated evidence that the enthalpy change for these systems will be from 2-4 kcal/mol more negative than the cobalt analogues. Compare, for example, horse coboglobin (-11.5 kcal/mol) to horse myoglobin (-15.0 kcal/mol) [4].

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