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Kinetics and Thermodynamics of the Reactions of Two Iron(III) Porphyrins with Imidazole and 1-Methylimidazole[1] in Dimethyl Sulfoxide

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Abstract: The reactions of tetraphenylporphinatoiron(III) chloride and hemin chloride with imidazole and 1-methylimidazole have been studied in dimethyl sulfoxide at μ = 0.04 M ($NaNO_3$). Stability constants have been determined for the reactions SFeP + 2L $\rightleftharpoons$ L_2FeP + S over a range of temperatures. There was no evidence for appreciable concentrations of LFeP in any of the systems studied. For $FeTPP^+$: $\Delta H^\circ = -10.7$ kcal/mol, $\Delta S^\circ = -13.8$ eu for imidazole and $\Delta H^\circ = -10.2$ kcal/mol, $\Delta S^\circ = -15.4$ eu for 1-methylimidazole. For hemin: $\Delta H^\circ = -8.0$ kcal/mol, $\Delta S^\circ = -4.6$ eu for imidazole and $\Delta H^\circ = -9.2$ kcal/mol, $\Delta S^\circ = -10.9$ eu for 1-methylimidazole. Although the thermodynamic parameters are quite similar for each of the metalloporphyrins with a given ligand, the kinetic features differ markedly. The hemin reactions are faster than those of $FeTPP^+$ and while $\tau^{-1} = k_f[L]^2 + k_r$ for $FeTPP^+$ with both ligands at all temperatures studied, for hemin the inverse relaxation time varies as $[L]^2$ at low concentrations of ligand only. At higher concentrations, the reaction approaches a first-order dependence on ligand. It is suggested that this more complicated kinetic profile for hemin reflects an alternative pathway to the formation of the diliganded adduct to the one applicable to the other iron(III) porphyrins thus far studied. For hemin, we suggest an activated complex in which the second ligand interacts with the iron atom *before* the spin state change has occurred.

The properties and reactivities of iron porphyrins are of considerable interest to chemists and biologists alike. The emphasis on iron porphyrins arises in part from the various roles these species play as prosthetic groups in the heme(Fe^{II})- and hemo(Fe^{III})proteins. Among the reactions displayed by these ubiquitous substances are oxygen binding for transport and storage as in the hemoglobins and myoglobins, electron transfer as in the cytochromes, and catalysis of peroxide decomposition (catalase) and activation (peroxidase). For several of these processes, the biological function of the metal porphyrin rests in part on its ability to exchange axial ligands. Thus many of the studies on model iron porphyrin systems have dealt with the thermodynamics and kinetics of axial ligand addition/substitution. However, mechanistic interpretations of previous studies of the kinetics of bonding of ligand molecules to iron(III) porphyrins have been obscured by complications such as mixed solvent media,[2] multiple forms of the attacking ligand and metalloporphyrin,[2,3] and the necessity of using micelles to solvate the porphyrin to prevent aggregation.[4] Even the NMR line broadening studies, which avoid the above difficulties, provide only a partial picture of axial ligation[5-11] since they yield information primarily on ligand dissociation kinetics.

The use of dimethyl sulfoxide as a solvent medium seems to effectively overcome many of the limitations of other investigations. A large number of iron porphyrins are soluble in this solvent; in the absence of added hydroxide there is little tendency for aggregation;[12] the aprotic nature of the solvent limits the number of metalloporphyrin and ligand forms which must be considered in discussing mechanistic pathways; the relatively high dielectric constant and donicity number of Me_2SO prevent extensive ion pairing in the medium and lead to solvent-coordinated metal sites;[13,14,15] and temperature-jump kinetic studies can be conveniently conducted using this solvent medium (cf. Figure 1). The reactions of iron(III) porphyrins with axial ligands are so rapid as to make the temperature-jump technique particularly useful for these investigations.

We are reporting on the thermodynamics and kinetics of the reactions of tetraphenylporphinatoiron(III) ($Fe^{III}TPP^+$) and hemin ($Fe^{III}PPIX^+$) with the ligands imidazole (Im) and 1-methylimidazole (1-CH_3Im) in a dimethyl sulfoxide medium. Both metalloporphyrins, in the absence of added nitrogenous bases, exist in solution as high-spin complexes in which the iron atom is significantly out of the plane defined by the pyrrole nitrogen atoms.[1,14,16] The coordination number of the iron

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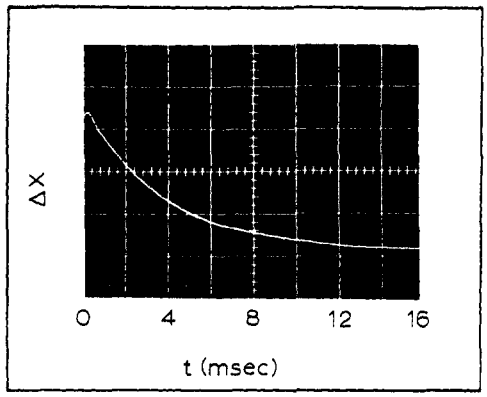


Figure 1. Relaxation effect obtained in Me_2SO for the hemin-imidazole system, [Im] = 1.2×10^{-2} M, μ = 0.04 M, temperature = 40 °C. The wavelength of observation was 400 nm.

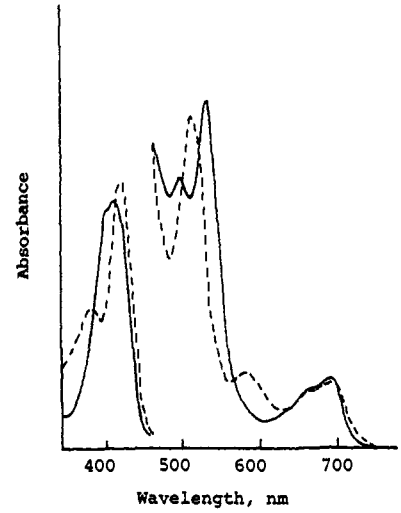
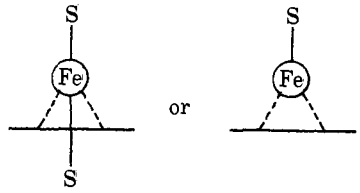


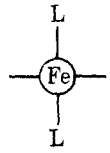
Figure 2. Comparison of spectra of FeTPPCl in chloroform (- - -) and dimethyl sulfoxide (—). The chloroform spectrum is typical of those obtained for FeTPPCl in noncoordinating solvents. The Soret peaks have been reduced by a factor of 10 relative to the visible bands.

atom is uncertain in such a coordinating solvent medium and structures involving five-coordinate[17] and six-coordinate[3,12,18] iron(III) have been used interchangeably, as, for example,



Thermodynamic results of ligand binding by iron(III) porphyrins in coordinating solvents are often interpreted in terms of the six-coordinate form in which there is a very weak interaction to a solvent molecule on the distal side of the porphyrin plane (vide infra). However, there is no direct experimental evidence for this conclusion and to emphasize the out-of-plane position of the iron atom and its strong bond to only one solvent molecule, we prefer to refer to this form as five-coordinate and use the symbol SFeP for it.

No such structural ambiguity exists for low-spin iron(III) porphyrin complexes for which the iron atom can be considered to be in plane.[16,19] These species are invariably six-coordinate and are usually of the form



although the two axial ligands need not be identical. For example, the monocyano mono-Me_2SO adduct of hemin is low spin[14] and evidence has been presented that the monohydroxo monoaquo form of tetra(4-*N*-methylpyridyl)porphineiron(III) is low spin in aqueous solution.[20,21]

The conversion of high-spin iron(III) porphyrin complexes to low-spin diliganded adducts is thought to proceed in two steps:[1,2,14,19,22-24]

$$SFeP + L \rightleftarrows LFeP \qquad K_1 = [LFeP]/[SFeP][L] \qquad (1)$$

$$LFeP + L \rightleftarrows L_2FeP \qquad K_2 = [L_2FeP]/[LFeP][L] \qquad (2)$$

although, with few exceptions, only the overall reaction is observed in thermodynamic studies:

$$SFeP + 2L \rightleftarrows L_2FeP \qquad \beta_2 = [L_2FeP]/[SFeP][L]^2 \qquad (3)$$

The failure to observe LFeP is taken as an indication that $K_2 \gg K_1$, which reflects that the change in spin state occurs with the addition of the *second* ligand.[19] An exception is the hemin-cyanide system[14] for which the monocyano adduct was shown to be low spin and, in this case, $K_1 > K_2$. For the systems reported on here we find no spectral nor thermodynamic evidence for the buildup of a monoliganded adduct, but kinetic evidence will be presented to establish its transitory existence.

Experimental Section

Tetraphenylporphine and tetraphenylporphinatoiron(III) chloride were synthesized by literature methods.[25,26] FeTPPCl was further purified by dry column chromatography using Fisher adsorption alumina. Two bands developed on the column; the first layer, which ran quickly through the column, was identified spectrally as FeTPPCl.[27] The second band proved to be the dimer, O-$(FeTPP)_2$,[28] which was converted to the monomer by shaking a benzene solution of the metalloporphyrin with 1.0 M HCl.

Aldrich imidazole was recrystallized three times from benzene; 1-methylimidazole was distilled from zinc dust, then potassium hydroxide, and was stored over Linde 4A molecular sieves. Aldrich dimethyl sulfoxide was stored over Linde 4A molecular sieves for 1 week before being distilled under vacuum. It was then stored over molecular sieves again until used. Fisher sodium nitrate (used to maintain constant ionic strength), Merck 3-(trimethylsilyl)propanesulfonic acid sodium salt (DSS), and ferriprotoporphyrin IX (hemin) chloride from Nutritional Biochemical Corp. were used without further purification.

Magnetic susceptibility measurements were made using the Evans' method[29] for FeTPPCl and hemin chloride in Me_2SO on a Varian T-60 NMR spectrophotometer with DSS as the reference. The susceptibilities for the 2:1 adducts of Im and 1-CH_3Im with $FeTPP^+$ and hemin in Me_2SO were also measured as a function of the ligand concentration. Spectral measurements were made on a Cary 14 spectrophotometer and kinetics experiments were conducted on a temperature-jump apparatus described previously.[30] The size of the temperature-jump as a function of voltage applied was determined by a combination of spectral and relaxation measurements with a $FeTPP^+$ solution in Me_2SO, μ = 0.04 M. Charging the high-voltage capacitor with 20 kV leads to a temperature increase of 4.7 °C for this medium.

Results

The spectra of FeTPPCl in a variety of noncoordinating solvents such as chloroform, methylene chloride, and ethyl acetate show marked similarities, as, for example, a β band at 510 ± 3 nm.[24] However, the spectrum of FeTPPCl in Me_2SO does not conform to the patterns found in these other solvents (cf. Figure 2) suggesting that, whereas a chloride ion occupies an axial position in noncoordinating solvents, the chloride ion is replaced by a solvent molecule in Me_2SO. The axial ligation

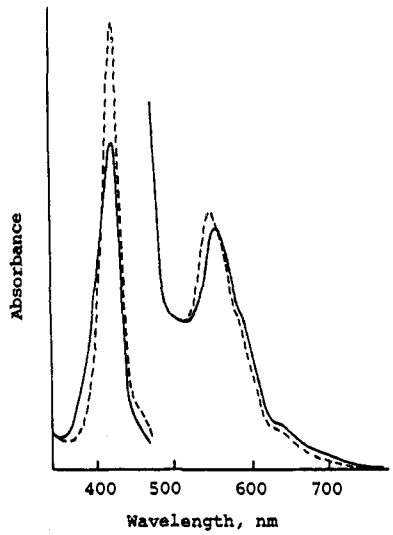


Figure 3. Comparison of spectra of the imidazole adducts of FeTPPCl in chloroform (- - -) and dimethyl sulfoxide (—). The Soret peaks have been reduced by a factor of 10 relative to the visible bands.

Table I. β_2 Values from Spectrophotometric Titrations (μ = 0.04 M)

Temp, °C	$FeTPP^+$ $\beta_2 \times 10^{-4}$	Hemin $\beta_2 \times 10^{-4}$
	A. Imidazole	
25	6.28	7.04
30	5.02	5.89
35	3.32	4.88
40	2.77	3.65
$\Delta H^\circ = -10.7 \pm 1.1$ kcal/mol		$\Delta H^\circ = -8.0 \pm 0.8$ kcal/mol
$\Delta S^\circ = -13.8 \pm 3.6$ eu		$\Delta S^\circ = -4.6 \pm 2.6$ eu
	B. 1-Methylimidazole	
25	1.28	2.44
30	0.965	1.98
35	0.762	1.53
40	0.554	1.14
$\Delta H^\circ = -10.2 \pm 0.5$ kcal/mol		$\Delta H^\circ = -9.2 \pm 0.7$ kcal/mol
$\Delta S^\circ = -15.4 \pm 1.5$ eu		$\Delta S^\circ = -10.9 \pm 4.6$ eu

of $FeTPP^+$ by a solvent molecule parallels the situation for hemin, for which it has been shown that, at concentrations below 0.01 M, only the Me_2SO adduct need be considered.[12,15] In the presence of excess imidazole and 1-methylimidazole, the spectra of FeTPPCl solutions are similar in Me_2SO to those in noncoordinating solvents (Figure 3) suggesting the presence of the same product chromophore in all solvents, the diliganded adduct. We will show later that this expectation is realized.

Beer's law behavior was obtained for the Me_2SO adducts of both $FeTPP^+$ and hemin at μ = 0.04 M over a concentration range of 10^{-6}–10^{-4} M. Furthermore, temperature-jump experiments showed no relaxation effects within the time range of the instrument (from ~55 μs to 200 ms), further suggesting that the metalloporphyrins are monomeric in solution.[31]

Spectrophotometric titrations of hemin and $FeTPP^+$ were conducted in the visible range at μ = 0.04 M with imidazole and 1-methylimidazole at 25, 30, 35, and 40 °C. Isosbestic points were obtained in all the titrations (Figure 4) and plots of $(A - A_0)/[L]^2$ vs. $-(A - A_0)$ were linear over the ligand concentration range (10^{-3} to 4×10^{-2} M) confirming that the product chromophore is the diliganded species in each case. (A_0 is the absorbance of the solution in the absence of added ligand and A is the absorbance when the ligand concentration

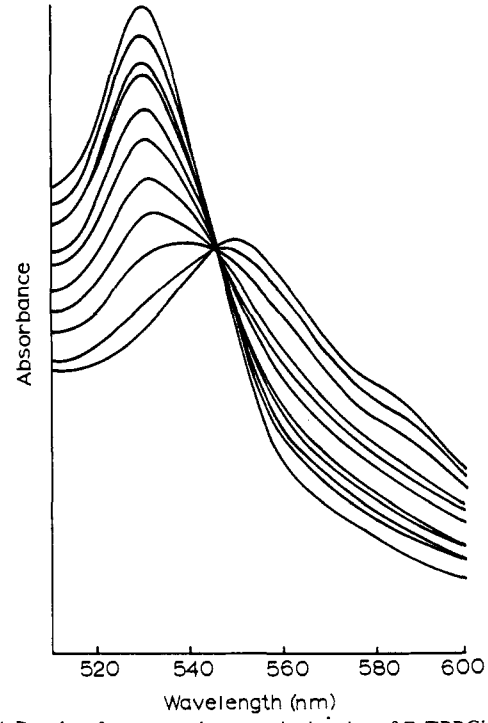


Figure 4. Results of a spectrophotometric titration of FeTPPCl with imidazole at 35.0 °C, μ = 0.04 M.

is [L].) The equilibrium constants

$$\beta_2 = \frac{[L_2FeP]}{[SFeP][L]^2} \tag{4}$$

were obtained using a general minimization routine, SIMPLEX,[32] as described earlier.[33] The working equation is

$$A - A_0 = \frac{\beta_2 \Delta\epsilon_2 [L]^2 C_0}{1 + \beta_2 [L]^2} \tag{5}$$

where C_0 is the total concentration of the metalloporphyrin and $\Delta\epsilon_2 = \epsilon_{L_2FeP} - \epsilon_{SFeP}$. The values obtained for all the systems studied are shown in Table I.

Magnetic susceptibility measurements for $FeTPP^+$ and hemin in Me_2SO without added nitrogenous base yielded values for the magnetic moments of 5.8 μ_B. This value is indicative of high-spin iron(III) involving five unpaired electrons. With the addition of either Im or 1-CH_3Im to $FeTPP^+$, the magnetic moments decrease with the conversion of the iron atom from a high-spin to a low-spin state. However, the diliganded forms of $FeTPP^+$ are not sufficiently soluble to permit precise measurements of the magnetic moment. A previous study, however, had found that in the presence of excess Im, the magnetic moment of $FeTPP(Im)_2^+$ is 1.8 μ_B in methylene chloride.[19] Because of the greater solubility of hemin in Me_2SO, the magnetic moments of the bisimidazole and bis-1-methylimidazole adducts could be determined as 3.0 and 2.9 μ_B, respectively.

The kinetics of the complexation reactions

$$SFeP + 2L \underset{k_r}{\overset{k_f}{\rightleftharpoons}} L_2FeP \tag{6}$$

were investigated using the temperature-jump technique. For $FeTPP^+$ plots of $1/\tau$ vs. $[L]^2$ are linear for both imidazole and 1-methylimidazole at all the temperatures studied; a typical set of results is shown in Figure 5. The reactions of hemin with imidazole and 1-methylimidazole have a somewhat different kinetic profile; $1/\tau$ varies as $[L]^2$ at low ligand concentration but as [L] at higher concentration (cf. Figure 6). A two-step pathway for the formation of the diliganded complex can account for the results for both metalloporphyrins:

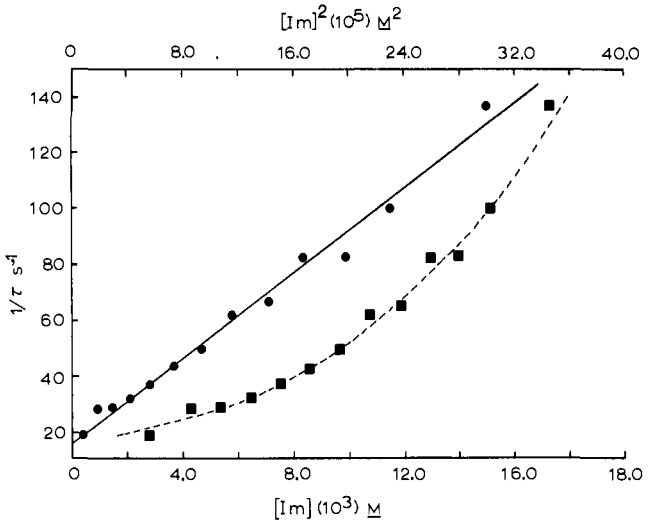


Figure 5. Plot of τ^{-1} vs. $[Im]^2$ (●) and vs. [Im] (■) at 25 °C, μ = 0.040 M for FeTPPCl in Me_2SO. The parabolic nature of the latter plot indicates that the kinetics have been studied over a sufficiently wide concentration range unambiguously to determine the order of the reaction with respect to imidazole.

Table II. Kinetic Results for $FeTPP^+$

Temp, °C	$k_1k_2/k_{-1} \times 10^{-5}$, M^{-2} s^{-1}	k_{-2}, s^{-1}
	A. Imidazole	
25	3.8	16
30	4.7	29
35	6.0	47
40	8.2	66
	k_1k_2/k_{-1}: $\Delta H^{\ddagger}$ = 9.0 ± 0.6 kcal/mol	
	$\Delta S^{\ddagger}$ = −2.7 ± 2.1 eu	
	k_{-2}: $\Delta H^{\ddagger}$ = 16.6 ± 1.2 kcal/mol	
	$\Delta S^{\ddagger}$ = 2.7 ± 3.8 eu	
	B. 1-Methylimidazole	
25	1.8	44
30	2.4	74
35	3.0	130
40	3.8	225
	k_1k_2/k_{-1}: $\Delta H^{\ddagger}$ = 8.6 ± 0.4 kcal/mol	
	$\Delta S^{\ddagger}$ = −5.7 ± 1.5 eu	
	k_{-2}: $\Delta H^{\ddagger}$ = 19.6 ± 0.5 kcal/mol	
	$\Delta S^{\ddagger}$ = 14.8 ± 1.7 eu	

$$SFeP + L \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} LFeP \quad (7)$$

$$LFeP + L \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} L_2FeP \quad (8)$$

We write the first step as a ligand replacement rather than addition (to form, for example, LSFeP) because of the spectral/thermodynamic result that LFeP is never present in appreciable concentration in solution, reflecting that the spin-state change occurs in the second step,[14,19] eq 8. As earlier, however, it is possible that there is a weak interaction of high-spin LFeP with a solvent molecule on the distal side of the porphyrin plane. By applying the steady-state approximation to LFeP and utilizing the experimental fact that $[L]_{total} \gg [FeP]_{total}$, we obtain

$$1/\tau = \frac{k_1k_2[L]^2/k_{-1} + k_{-2}}{1 + k_2[L]/k_{-1}} = \frac{k_{-2}(1 + \beta_2[L]^2)}{1 + k_2[L]/k_{-1}} \quad (9)$$

Apparently for $FeTPP^+$, $k_2[L]/k_{-1} \ll 1$ for all ligand concentrations yielding relaxation data and

$$1/\tau = k_1k_2[L]^2/k_{-1} + k_{-2} \quad (10)$$

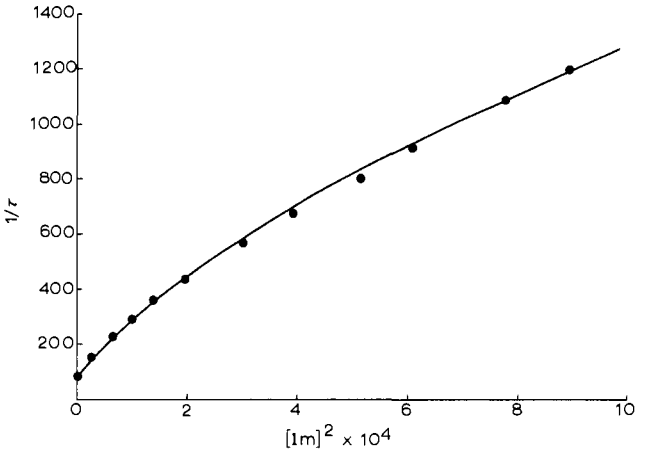


Figure 6. Plot of τ^{-1} vs. $[Im]^2$ at 35 °C, μ = 0.040 M for FePPIXCl in Me_2SO. The curve shown was generated from eq 9 with $k_1 = 5.7 \times 10^4$ M^{-1} s^{-1}, k_2/k_{-1} = 68 M^{-1}, and k_{-2} = 80 s^{-1}.

Table III. Kinetic Results for Hemin

Temp, °C	$k_1 \times 10^{-4}$, M^{-1} s^{-1}	k_2/k_{-1}, M^{-1}	k_{-2}, s^{-1}
	A. Imidazole		
25	2.3	141	47
30	4.3	95	69
35	5.7	68	80
40	8.2	58	130
	k_1: $\Delta H^{\ddagger}$ = 14.6 ± 1.8 kcal/mol		
	$\Delta S^{\ddagger}$ = 11.7 ± 6.2 eu		
	k_2/k_{-1}: ΔH° = −11.2 ± 1.3 kcal/mol		
	ΔS° = −27.6 ± 4.3 eu		
	k_{-2}: $\Delta H^{\ddagger}$ = 11.3 ± 1.7 kcal/mol		
	$\Delta S^{\ddagger}$ = −13.1 ± 5.6 eu		
	B. 1-Methylimidazole		
25	4.2	75	130
30	5.5	65	180
35	7.2	57	270
40	8.6	47	355
	k_1: $\Delta H^{\ddagger}$ = 8.4 ± 0.8 kcal/mol		
	$\Delta S^{\ddagger}$ = −9.4 ± 2.7 eu		
	k_2/k_{-1}: ΔH° = −5.7 ± 0.6 kcal/mol		
	ΔS° = −10.6 ± 2.2 eu		
	k_{-2}: $\Delta H^{\ddagger}$ = 12.1 ± 0.9 kcal/mol		
	$\Delta S^{\ddagger}$ = −8.4 ± 2.9 eu		

Table II shows the results of the kinetic experiments for $FeTPP^+$ with imidazole and 1-methylimidazole. For hemin, the inequality shown above is not applicable throughout the ligand concentration region and the complete expression 9 must be used to fit the data. The curve shown in Figure 6 is calculated from eq 9 using the spectroscopically obtained equilibrium constant, β_2. The kinetic data for hemin are summarized in Table III.

Discussion

Spectral and conductivity[12] evidence has been presented to indicate that the stable forms of FePPIXCl and FeTPPCl in Me_2SO, in the absence of added Lewis base, involve an axially bonded solvent molecule in place of a chloride ion. Chloride coordination is generally found in noncoordinating solvents such as chloroform, methylene chloride, and ethyl acetate.[19,24] Thermodynamic studies on ligand binding in noncoordinating solvents lead to standard state entropy values of about −45 eu (cf. Table IV). In contrast, as may be seen from this table, for coordinating solvents having high dielectric constants (such as Me_2SO and H_2O) entropy values of −5 to −15 eu are more typical. This difference may reflect the lack of extensive ion pairing between the L_2FeP^+ complex and chloride ion in

Table IV. Thermodynamic Parameters for Ligand Bonding to Iron(III) Porphyrins

Metalloporphyrin	Ligand	Solvent	β_2 (25 °C)	$\Delta H°$	$\Delta S°$	Ref
FeTPPCl	Im	$CH_3C(O)CH_3$	5.8×10^4	−20	−44	24
		$CHCl_3$	8.2×10^5	−23	−48	24
		CH_2Cl_2	5.9×10^5	−22	−45	24
		$CH_3COOC_2H_5$	2.9×10^3	−18	−44	24
		Me_2SO	6.3×10^4	−11	−14	This work
	1-CH_3Im	Me_2SO	1.3×10^4	−10	−15	This work
Fe(deut)Cl	Im	CH_2Cl_2	7.8×10^5	−22	−46	34
FePPIXCl	Im	Me_2SO	7.0×10^4	−8	−5	This work
	1-CH_3Im	Me_2SO	2.4×10^4	−9	−11	This work
Hemin c	Im	H_2O	1.0×10^6	−11	−9	35
	py	H_2O	1.1×10^3	−8	−13	35

Table V. Equilibrium Constants for Ligand Bonding to Metal(III) Porphyrins

Ligand	Solvent	Metalloporphyrin	β_2 (25 °C)	Ref
1-CH_3Im	$CDCl_3$	Fe(*p*-CH_3O-TPP)Cl	4.0×10^3	22
	$CDCl_3$	Fe(*p*-CH_3-TPP)Cl	3.0×10^3	22
	$CDCl_3$	Fe(TPP)Cl	1.4×10^3	22
	$CDCl_3$	Fe(*p*-ClTPP)Cl	0.65×10^3	22
	Me_2SO	Fe(TPP)Cl	1.3×10^4	This work
	Me_2SO	Fe(PPIX)Cl	2.4×10^4	This work
Im	$CHCl_3$	Fe(TPP)Cl	8.2×10^5	24
	Me_2SO	Fe(TPP)Cl	6.3×10^4	This work
	Me_2SO	Fe(PPIX)Cl	7.0×10^4	This work
	H_2O	Na_3(FeTPPS)	1.4×10^7	36
	H_2O	Fe(TMpyP)Cl_5	2.5×10^7	36
SCN^-	H_2O	Na_3(CoTCPP)	1.8×10^4	37
	H_2O	Co(TMpyP)Cl_5	8.3×10^4	33a
py	H_2O	Na_3(FeTPPS)	4.3×10^3	33b
	H_2O	Fe(TMpyP)Cl_5	3.1×10^3	36
	H_2O	Na_3(CoTCPP)	$\sim 10^{11}$	37
	H_2O	Co(TMpyP)Cl_5	4.8×10^{10}	33a

Me_2SO and H_2O.[12,13] In solvents of low dielectric constant, the chloride ion is not totally freed from the iron porphyrin complex even when replaced at an axial position. A second contributing factor may be related to the coordination number of high-spin iron porphyrins in coordinating and noncoordinating solvents as alluded to earlier. While in noncoordinating solvents the iron atom is almost certainly five-coordinate, in solvents such as Me_2SO and H_2O the iron atom may well be six-coordinate with one iron–solvent bond much weaker than the other. The release of two axial ligands (as in coordinating solvents) rather than one (as in noncoordinating solvents) would make the entropy of complex formation less unfavorable in the former solvents.

$$ClFeP + 2L \rightleftarrows L_2FeP, Cl \qquad (11)$$

A subject of some interest is the influence of peripheral substituents on the stabilities of metalloporphyrin complexes with a given ligand. For example, the stability constants for the binding of 1-CH_3Im to a number of iron(III) tetraphenylporphine derivatives have been measured in chloroform.[22,23] A summary of the results is shown in Table V. The decrease in β_2 with increasing electron-withdrawing tendency of the para substituent has been interpreted as indicating the importance of the stabilization of the positive charge on Fe(III) in the product complex.[22,23] However, the most striking feature of the thermodynamic data shown in Table V is the remarkable similarity of the equilibrium constants measured in a given solvent for a given ligand with a variety of iron(III) porphyrin derivatives. The water-soluble species tetraphenylporphinesulfonatoferrate(III) (FeTPPS) and tetra(4-*N*-methylpyridyl)porphineiron(III) (FeTMpyP) are a case in point. The p*K* of H_4TPPS^{2-} is about 4.8[38] while that for H_4TMpyP^{6+} is 2.5–2.7.[39,40] Yet the stability constants for the two metalloporphyrins are virtually identical for a given ligand (pyridine or imidazole). Similar patterns emerge for the cobalt(III) derivatives of tetracarboxyphenylporphine (TCPP) and TMpyP. Although the p*K*s of the porphyrins differ by about two to three units, the stability constants for a given ligand agree to well within a factor of 10. The generalization which might be made concerning these results is that even fairly substantial modifications at the periphery of the metalloporphyrin do not lead to pronounced changes in the stability constants of cobalt(III) nor iron(III) derivatives which severely limits what can be learned about differences among iron(III) and cobalt(III) porphyrins from stability constants alone.

In contrast, the kinetics of ligand addition/substitution are very sensitive to porphyrin peripheral substituents. The rates of substitution of ligands for axial water molecules for CoTCPP are orders of magnitude faster than the corresponding reactions for CoTMpyP[33,37] while the ligation reactions of monomeric FeTPPS are much faster than those for FeTMpyP.[36] Similarly, although the equilibrium constants for either imidazole or 1-methylimidazole are nearly identical for FeTPPCl and FePPIXCl in Me_2SO, the kinetic profiles for adduct formation are quite different for the two metalloporphyrins. Whereas for FeTPPCl the addition of the second nitrogeneous ligand with the concomitant spin-state change is rate determining throughout the concentration range ($k_{-1} \gg k_2[L]$), such is not the case for FePPIXCl.

Turning first to the kinetic results for hemin (Table III), we find very little difference in k_1 values for the two ligands, imidazole and 1-methylimidazole, at any given temperature. It should be noted that these values are obtained from computer fitting of the data and comparisons must be approached with some caution since the values are not arrived at independently of other parameters of the system (as are, for example, values

Table VI. Kinetic Comparison of $FePPIX^+$ and $FeTPP^+$

Temp, °C	$FePPIX^+ + Im$ $k_1k_2/k_{-1} \times 10^{-6}$	$FeTPP^+ + Im$ $k_1k_2/k_{-1} \times 10^{-5}$	$FePPIX^+ + 1\text{-}CH_3Im$ $k_1k_2/k_{-1} \times 10^{-6}$	$FeTPP^+ + 1\text{-}CH_3Im$ $k_1k_2/k_{-1} \times 10^{-5}$
25	3.2	3.8	3.2	1.8
30	4.1	4.7	3.6	2.4
35	3.9	6.0	4.1	3.0
40	4.8	8.3	4.1	3.8
	$\Delta H^{\ddagger}$ = +3.4 kcal/mol $\Delta S^{\ddagger}$ = −16 eu	$\Delta H^{\ddagger}$ = 9.4 kcal/mol $\Delta S^{\ddagger}$ = −3 eu	$\Delta H^{\ddagger}$ = 2.7 kcal/mol $\Delta S^{\ddagger}$ = −20 eu	$\Delta H^{\ddagger}$ = 8.6 kcal/mol $\Delta S^{\ddagger}$ = −6 eu

Table VII. Ligand Dissociation Rate Constants and Activation Parameters

Species	Solvent	k_{-2} (25 °C)	$\Delta H_{-2}^{\ddagger}$	$\Delta S_{-2}^{\ddagger}$	Ref
$FeTPP(Im)_2$	Me_2SO	16	17	4	This work
$FeTPP(1\text{-}CH_3Im)_2$	Me_2SO	44	20	15	This work
$FeTPP(1\text{-}CH_3Im)_2$	$CDCl_3$	60	16	7	10
$FeOEP(1\text{-}CH_3Im)_2$[a]	$CDCl_3$	950	17	17	8
$hemin(Im)_2$	Me_2SO	47	11	−13	This work
$hemin(1\text{-}CH_3Im)_2$	Me_2SO	130	12	−8	This work
$hemin(py)(H_2O)$	py/H_2O	py 3×10^4	8.4	−10	11
		H_2O 5×10^3	7.4	−16	11
$hemin(C_2H_5OH)(OH)$	C_2H_5OH/H_2O	1.8×10^6	6.2	−9	9
$heminDME(py)_2$[a]	$py/CDCl_3$	2×10^3	9	−13	7

[a] Abbreviations: OEP = octaethylporphine; DME = dimethyl ester.

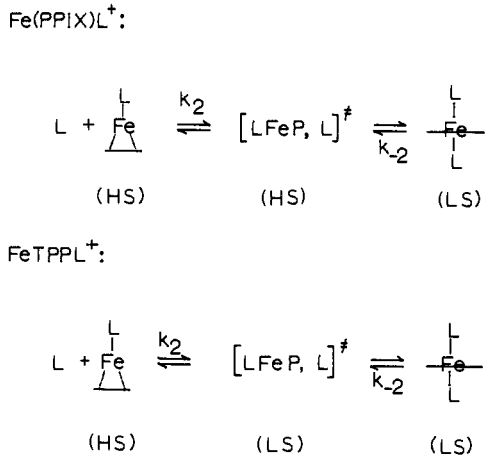


Figure 7. Suggested mechanisms for ligand addition to $Fe(PPIX)L^+$ and $FeTPPL^+$.

of k_{-2} which can be obtained directly from extrapolations of the observed rate profiles). The similarities in k_1 for the two ligands suggest a dissociative pathway for this step, although it would be quite useful to study the kinetics of adduct formation of $FePPIX^+$ with ligands having very different stability constants than those for Im or $1\text{-}CH_3Im$.

An informative comparison involves the k_2/k_{-1} and k_{-2} values for the two metalloporphyrins. The deviation of the forward rate constant from second-order dependence on ligand for hemin reflects a larger value of the ratio k_2/k_{-1} for this metalloporphyrin than for $FeTPP^+$; the ligand concentration range was virtually identical for the two porphyrins. A direct comparison of the kinetic results for the two metalloporphyrins can be made by considering the product of k_1 and k_2/k_{-1} for hemin as is shown in Table VI. The results indicate that k_1k_2/k_{-1} is about an order of magnitude larger for hemin than the respective value for $FeTPP^+$ and that the activation parameters (which are more reliable than those shown for k_1 alone) are quite similar for both ligands with a given metalloporphyrin but differ markedly for the two porphyrins. Since stability constants are not very sensitive to modifications in porphyrin structure (vide supra), we suggest that these differences reflect variations in k_2 rather than in the ratio $k_1/k_{-1} = K_1$. Thus, we conclude that for hemin, the activation energy for the second ligand addition is much smaller and the entropy of activation more unfavorable than for $FeTPP^+$. We see a very similar pattern emerge for the k_{-2} values; the enthalpies of activation are considerably smaller for hemin than for $FeTPP^+$ while the entropies of activation are substantial and negative for hemin but positive for $FeTPP^+$. A comparison of these results with other published work is shown in Table VII. The differences between the activation parameters for hemin and those for $FeTPP^+$ and $FeOEP^+$ are striking; the results suggest an associative-type mechanism for hemin but a dissociative-type mechanism for $FeTPP^+$ and $FeOEP^+$. However, it is difficult to correlate the apparent change in mechanism with other properties of the porphyrin ligands. The fact that tetraphenylporphyrin is a meso-substituted porphyrin having bulky substituents perpendicular to the porphyrin ring system seems immaterial because octaethylporphine resembles protoporphyrin IX structurally more closely than it does tetraphenylporphine. The ligand basicity does not seem central either since H_2PPIX is more basic than H_2TPP but less basic than H_2OEP.[41]

An alternative explanation for the unique activation parameters for hemin can be offered which does not require major differences in the mechanisms for adduct formation for the various metalloporphyrins. The experimental basis for this suggestion arises from NMR and magnetic susceptibility measurements as described below. Hambright and co-workers[42] determined the magnetic susceptibilities of a number of iron(III) porphyrin complexes and found that the magnetic moments for bis(imidazole)mesohemin and bis(imidazole)-deuteriohemin are ~2.3 μ_B. However, for bis(imidazole)protohemin ($FePPIX(Im)_2^+$) a value of 3.1 μ_B was obtained. In the present study, we obtained values of ~3 μ_B for the diliganded complexes of protohemin as well. A magnetic moment of 2.0–2.4 μ_B is the "normal" value for diliganded iron(III) porphyrins as determined for a number of systems including $Fe^{III}TPP(Im)_2$.[43] Hambright et al. have suggested, on the basis of these experiments, that the diliganded form of protohemin exists at or near room temperature as an equilibrium system involving a high-spin and a low-spin form. Similar conclusions were reached by Hill and Morallee,[44] by Goldammer and

Zorn[6] for the bispyridine complex, and by Degani and Fiat[11] for the mixed pyridine/aquo complex of protohemin. Therefore, for diliganded forms of $FePPIX^+$ a high-spin state is accessible and populated at room temperature. Furthermore, it has been shown that for the process[6,11]

$$\text{low spin} \rightarrow \text{high spin}$$

$\Delta H^{\ddagger} \sim 5$–$6$ kcal/mol and $\Delta S^{\ddagger} \sim -30$ eu.

From the available information we suggest the mechanism shown in Figure 7 to account for the differences between $FeTPP^+$ and hemin. For $FePPIX^+$ with its accessible high-spin state for the diliganded species, we envision an activated complex in which the second imidazole (or 1-methylimidazole) ligand interacts with the iron atom *before* the spin-state change has occurred. This interaction facilitates the spin state conversion for hemin. Considering the reverse process, although the k_{-2} step is dissociative for both metalloporphyrins, $\Delta S^{\ddagger}$ is negative for hemin because a spin-state change (low spin → high spin) occurs en route to the activated complex. Conversely, for the k_2 step, the spin-state change (high spin → low spin) for $FeTPP^+$ makes the activation energy higher but the entropy of activation more favorable than for hemin. It is the availability of this alternative pathway to adduct formation for hemin which we suggest makes the value of k_2 and, hence, k_2/k_{-1} large relative to $FeTPP^+$.

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