

where $K_8 = [8](H^+)/[8']$, $K_9 = [9](H^+)/[9']$, and $K_{89} = [9](H^+)/[8]$. With the reasonable assumption that K_8 , $K_9 \gg (H^+)$, and since $K_{13} \approx (H^+)$, therefore $K_{89} > (H^+)$, and $k_{9'3} \approx k_{8'2} \gg k_{82}$ and $k_{9'10} \approx k_{9'10'}$. These conditions show that the last term in the numerator of the above two equations are the dominant ones. It seems likely, for reasons discussed in regard to cysteine, that $K_9 > 10^{-2}$, therefore $k_{de} > k_{da}$ as long as $k_{9'3} < 10^4 k_{9'10}$. If this condition is satisfied then

$$k'_{\text{obsd}} = k_{\text{ag}} + k_{\text{ad}} = \frac{k_{3,11}K_{13}}{(H^+) + K_{12} + K_{13}}[M] + \frac{k_{19}(H^+) + k_{28}K_{12} + k_{39}K_{13}}{(H^+) + K_{12} + K_{13}}[M] \quad (\text{B10})$$

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- (20) This assumption and those used to derive eq 8 and 9, can be justified by substitution of rate constant values derived later in this work. Calculations, using eq 5, show that $\gamma_- \geq 10^2 \gamma_+$, and γ_- is much larger than experimental values. Generally, γ_- is dominated by a_2 , which is independent of $[M]$, while experimental values are first order in $[M]$. The approximations will become less valid as pK_1 decreases, and pH and $[M]$ increase; conservative limits seem to be pH < 7, $pK_1 \approx 6$, and $[M] < 0.1 M$ and pH < 7, $pK_1 \approx 8$, and $[M] < 0.3 M$ etc., for nickel(II) systems at least.
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Electronic Effects in Transition Metal Porphyrins. I. The Reaction of Piperidine with a Series of Para- and Meta-Substituted Nickel(II) and Vanadium(IV) Tetraphenylporphyrins¹

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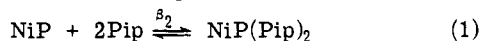
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Abstract: Para- and meta-substituted tetraphenylporphyrin complexes of Ni(II), Ni(*p*-X)TPP and Ni(*m*-X)TPP (X = OCH₃, CH₃, H, F, Cl, COOCH₃, CN, and NO₂), and para-substituted V(IV) tetraphenylporphyrins, VO(*p*-X)TPP (X = OCH₃, CH₃, H, Cl, and CN), react in the presence of high concentrations of piperidine in toluene to form the bis- and monopiperidine adducts, respectively Ni(X)TPP + 2Pip \rightleftharpoons Ni(X)TPP(Pip)₂ (β_2) and VO(X)TPP + Pip \rightleftharpoons VO(X)TPP(Pip) (K_1^V). In most cases, equilibrium constants β_2 and K_1^V are less than unity. For reactions 1 and 2 a Hammett $\sigma\rho$ relationship is observed, with $\rho^{Ni(p)} = 0.331$, $\rho^{Ni(m)} = 0.413$, and $\rho^V = 0.113$. Thus substituents at such remote positions as the meta and para positions of the phenyl rings significantly affect the axial reactivity of the metal. The extent of this effect is greatly increased if the metal has a full complement of *d*π electrons (Ni(II), d⁸, as compared to V(IV), d¹). Inductive and resonance contributions to the observed substituent effects are almost equal when X is in the para position, but inductive effects predominate when X is in the meta position. Either π induction or moderate π conjugation between phenyl and porphine rings (or a combination of both) may be the mode of transmission of resonance effects. In dilute piperidine solutions, NiTPP reacts to give the monopiperidine complex, whose electronic spectrum is almost indistinguishable from that of the reactant. ESR splitting constants and *g* values of the VO(*p*-X)TPP complexes and their piperidine adducts are independent of the substituent X.

The transmission of electronic effects from various points on the porphyrin ring through the four porphyrin nitrogens to the metal ion has long been an interest of those who have investigated the physical properties and chemical reactions of metalloporphyrins.²⁻⁵ Because of the conjugated nature of the porphyrin ring system, electron donating or withdrawing substituents on the periphery of the molecule have

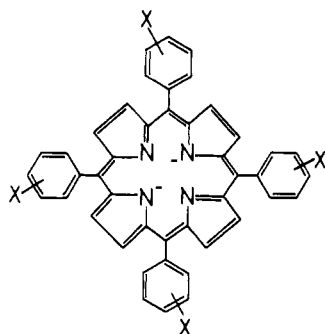
been shown to affect the basicity of the porphyrin nitrogens.^{2,3} This, in turn, often affects the visible absorption spectra, redox potentials, and axial ligation reactions of the free bases and their respective metalloporphyrin complexes.^{2,4,5} Some of the most detailed investigations of the transmission of electronic effects in metalloporphyrins have been carried out on Ni(II) complexes of natural or modified

natural porphyrins by Caughey and coworkers.⁴ They have shown that the position of the equilibrium



where P = various porphyrins and Pip = piperidine, is dependent upon the electron withdrawing or electron donating characteristics of the substituents on the porphyrin, P. Thermodynamic parameters for reaction 1 where P = a series of 2,4-disubstituted deuteroporphyrins in chloroform solution have been reported.^{4a} It was shown that $\log \beta_2$ (reaction 1) was linearly related to the $\text{p}K_b$ of the deuteroporphyrin free base.

In an attempt to further quantify the effect of electron donating or withdrawing substituents on reaction 1, and to assess the importance of the phenyl groups of tetraphenylporphyrins on the reactivity of the metal, the investigation of this reaction, where P = a series of meta- or para-substituted tetraphenylporphyrins, (*m*- or *p*-X)TPP, structure I, was undertaken.

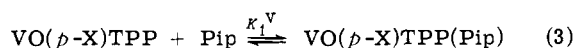


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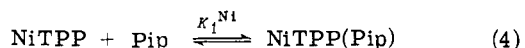
The rates and equilibria of many such reactions of substituted aromatics are known to follow the Hammett relationship,⁶ which, for reaction 1, may be written as

$$\log (\beta_{2X}/\beta_{2H}) = \sigma \rho \quad (2)$$

Thus, in the reaction of Lewis bases with $\text{M}(\text{X})\text{TPP}$, the questions to which we have sought answers in this work are the following. How sensitive is a reaction at the metal center to electronic effects of phenyl substituents on the porphyrin ring? How does the number of d electrons on the metal affect the sensitivity of the metal to the electronic effects? Are these effects transmitted through the σ or the π system of the porphyrin ring? Associated with this question is that of the degree of conjugation of the phenyl rings with the porphyrin π system. In order to answer these questions, two series of metal porphyrin complexes were chosen: $\text{Ni}(\text{m- or p-X})\text{TPP}$, in which the metal contained a full complement of d_{π} electrons for interaction with the π or π^* orbitals of the porphyrin ring, and $\text{VO}(\text{p-X})\text{TPP}$, in which the metal did not contain electrons in proper symmetry orbitals for interaction with the π or π^* orbitals of the porphyrin. The series of $\text{Ni}(\text{m- or p-X})\text{TPP}$ react with piperidine according to eq 1, where P = (*m*-X)TPP or (*p*-X)TPP, while the $\text{VO}(\text{p-X})\text{TPP}$ complexes add only 1 mol of piperidine.



In addition, the reaction of NiTPP with 1 mol of piperidine



was also investigated in order to clarify the spectral changes and stoichiometry of reaction of piperidine with $\text{Ni}(\text{II})$ porphyrins.

Because four substituents X are present in the systems of this investigation (structure I), eq 2 will be written as

$$\log (\beta_{2X}/\beta_{2H}) = (4\sigma)\rho \quad (2a)$$

Experimental Section

The meta- and para-substituted tetraphenylporphyrin free bases, $\text{H}_2(\text{m-X})\text{TPP}$ and $\text{H}_2(\text{p-X})\text{TPP}$, where X = OCH_3 , CH_3 , H, F, Cl, COOH , CN, and NO_2 , were prepared by the method of Adler et al.⁷ The $\text{H}_2(\text{p-COOH})\text{TPP}$ was esterified in methanol- H_2SO_4 by the method of Falk⁸ and then chromatographed on silica gel (Baker chromatographic grade) with chloroform as solvent to remove porphyrin which contained remaining free carboxyl groups. All of the other substituted tetraphenylporphyrins were chromatographed in like manner at least once before metal insertion.

Formation of the $\text{Ni}(\text{II})$ and $\text{V}(\text{IV})$ complexes of the substituted tetraphenylporphyrins was accomplished by the method of Adler et al.⁹ Considerable difficulty was encountered in obtaining complete reaction of the porphyrin free bases in dimethylformamide, even after prolonged heating in the presence of large (100-fold) excesses of $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ or $\text{VOSO}_4 \cdot x\text{H}_2\text{O}$ (Alfa Inorganics). In several cases, addition of detergents such as sodium lauryl sulfate appeared to aid in the insertion of $\text{Ni}(\text{II})$.¹⁰ Complete reaction was assumed when the free base absorption peak at 650 nm had disappeared.

All $\text{Ni}(\text{II})$ and $\text{V}(\text{IV})$ complexes were chromatographed in the same manner as the $\text{H}_2(\text{m- or p-X})\text{TPP}$ before use. Anal. Calcd for $\text{C}_{48}\text{H}_{36}\text{N}_4\text{Ni}$: C, 79.24; H, 4.99; N, 7.70; Ni, 8.07. Found: C, 78.89; H, 4.94; N, 7.96; Ni, 8.02 (analysis by Galbraith Laboratories, Knoxville, Tenn).

Piperidine was distilled from zinc dust and then barium oxide, and toluene was distilled from calcium hydride shortly before use.

Equilibrium constants for formation of the monopiperidine complexes of the series of $\text{VO}(\text{p-X})\text{TPP}$ complexes (reaction 3)

$$K_1^V = [\text{VO}(\text{p-X})\text{TPP}(\text{Pip})]/[\text{VO}(\text{p-X})\text{TPP}][\text{Pip}] \quad (5)$$

and for formation of the bispiperidine adducts of $\text{Ni}(\text{m- or p-X})\text{TPP}$ (reaction 1)

$$\beta_2 = [\text{Ni}(\text{X})\text{TPP}(\text{Pip})_2]/[\text{Ni}(\text{X})\text{TPP}][\text{Pip}]^2 \quad (6)$$

were measured in toluene solution on a Cary 14 spectrophotometer equipped with a circulating constant temperature bath. Calculation of β_2 was carried out by the method of Bent and French¹¹ and checked by the method and criteria of Drago and coworkers.¹² Calculation of K_1^V was carried out entirely by the method of Drago et al.¹²

Because of the insolubility of many of the $\text{M}(\text{m- or p-X})\text{TPP}$ compounds (a saturated solution of $\text{Ni}(\text{p-CN})\text{TPP}$ is about $2.7 \times 10^{-6} M$), stock solutions were prepared in many cases by heating excess $\text{M}(\text{m- or p-X})\text{TPP}$ in toluene for about 1 hr, allowing the solution to stand at room temperature for at least 1 day, and filtering the solution before use. It was not necessary to know the concentration of the $\text{M}(\text{m- or p-X})\text{TPP}$ stock solution because $[\text{Pip}]_{\text{eq}} \approx [\text{Pip}]_0$ in all cases. Spectrophotometric cells of 10 cm, 1 cm, or 1 mm path length were utilized as required. Since aggregation is insignificant in the nonaqueous solution behavior of tetraphenylporphyrins at concentrations typical of ESR¹³ ($10^{-3} M$) and NMR¹⁴ (10^{-2} to $10^{-1} M$) investigations, it is not expected to influence the equilibrium constant measurements by visible spectral techniques (10^{-4} to $10^{-5} M$).

The addition of one molecule of piperidine to NiTPP , eq 4, was investigated by observing difference spectra on the 0.1 absorbance scale of a Cary 1501 spectrophotometer utilizing 1-cm path length cuvettes. Solutions $1.93 \times 10^{-5} M$ in NiTPP in which the sample cell contained concentrations of piperidine ranging from 5×10^{-4} to $4 \times 10^{-2} M$ were investigated at the ambient temperature of 22°. Maximum absorbance differences were observed at 437.6 nm.

The ESR spectra of the $\text{VO}(\text{p-X})\text{TPP}$ complexes were measured at 100 and -196° in toluene and piperidine on a Varian E-12 ESR spectrometer. Varian weak pitch ($g = 2.0027$) was used as field-frequency calibrant, and the field sweep width was calibrated by use of an NMR gaussmeter, Alpha Model AL 675.

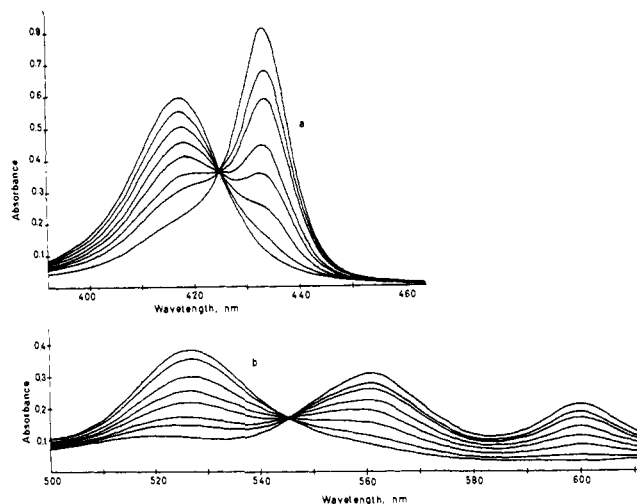


Figure 1. Visible spectra of Ni(*p*-CH₃)TPP in the presence of varying amounts of piperidine. [Ni(*p*-CH₃)TPP] = 4×10^{-5} M: (a) cell path length = 1 mm; (b) cell path length = 1 cm. Typical absorption maxima and extinction coefficients of the four- and six-coordinate complexes are given in the Results section.

Results

The absorption spectra of Ni(*m*- or *p*-X)TPP (Figure 1, X = *p*-CH₃) and VO(*p*-X)TPP (Figure 2, X = CH₃) change dramatically upon addition of large amounts of piperidine. Typical absorption maxima and extinction coefficients for Ni complexes are 527.7 ($\epsilon 9.50 \times 10^3$) and 415.7 nm ($\epsilon 1.36 \times 10^5$) for Ni(*p*-Cl)TPP and 600.0 ($\epsilon 5.35 \times 10^3$), 561.2 ($\epsilon 7.96 \times 10^3$), and 433.5 nm ($\epsilon 2.04 \times 10^5$) for Ni(*p*-Cl)TPP(Pip)₂. Peak positions of other meta- and para-substituted NiTPP complexes differed by less than 1 nm and showed no obvious relationship to the donating or accepting nature of the substituent. Similarly, vanadyl porphyrin complexes showed little dependence of peak positions on substituent. VO(*p*-CH₃)TPP has absorption peaks at 425 ($\epsilon 4.77 \times 10^5$), 549 ($\epsilon 2.17 \times 10^4$), and 587 nm ($\epsilon 2.73 \times 10^3$); other para-substituted vanadyl complexes gave absorption peaks which were within 4 nm (425-nm peak) or 1 nm of the values for the *p*-CH₃ complex, and no linear dependence on the substituent constant of X was noted. VO(*p*-CH₃)TPP(Pip) has absorption peaks at 438 ($\epsilon 4.78 \times 10^5$), 563 ($\epsilon 1.74 \times 10^4$), and 605 nm ($\epsilon 9.74 \times 10^3$).¹⁵

Calculation of β_2 or K_1^V was carried out at each of the above wavelengths except the 588-nm peak of VO(*p*-X)TPP. Average values of the constant were obtained at each wavelength, and in general the values of the constants obtained at the five wavelengths in each case were in excellent agreement (5% or better). Only the *p*-CN and *p*-NO₂ complexes were so insoluble as to restrict measurement of the equilibrium constants to only the wavelengths of the most intense peak (Soret band) of reactant and product. The equilibrium constants reported in Tables I–IV are the average of those values obtained at the individual wavelengths. The logarithmic method¹¹ was used for determination of β_2 for reaction 1 for two reasons: (a) the limiting spectrum of the product could be measured, or estimated to high accuracy, thus eliminating the problem of an equation with two unknowns, and (b) in order to determine, without imposing conditions upon the experimental data, the number of ligands involved in the reaction.¹⁶ In the present case, since β_2 was small, eq 6 could be rewritten as

$$\beta_2 = ((A_1 - A_0)/(A_c - A_1))[\text{Pip}]^{-2} \quad (7)$$

where A_0 = absorbance of a solution of Ni(X)TPP in the absence of piperidine, A_c = absorbance of a solution of the

Table I. Equilibrium Constants for Addition of Two Piperidines to Ni(*p*-X)TPP^a ($\rho^{\text{Ni}(p)} = 0.331 \pm 0.005$)

Para substituent	σ_X^b	n	Log β_2X	Corr coeff
OCH ₃	-0.268	2.03 ± 0.04	-0.69 ± 0.04	0.998
CH ₃	-0.170	1.94 ± 0.03	-0.60 ± 0.03	0.998
H	0.000	1.94 ± 0.03	-0.37 ± 0.03	0.999
F	0.062	2.07 ± 0.04	-0.29 ± 0.01	0.999
Cl	0.227	1.91 ± 0.04	-0.12 ± 0.07	0.996
COOCH ₃	0.450	1.96 ± 0.05	0.21 ± 0.07	0.996
CN	0.660	1.97 ± 0.05	0.56 ± 0.06	0.997
NO ₂	0.778	1.99 ± 0.05	0.65 ± 0.04	0.997

^aSolvent = toluene, temperature = 22°. ^bReference 5.

Table II. Equilibrium Constants for Addition of Two Piperidines to Ni(*m*-X)TPP^a ($\rho^{\text{Ni}(m)} = 0.413 \pm 0.06$)

Para substituent	σ_X^b	n	Log β_2X	Corr coeff
OCH ₃	0.12	1.97 ± 0.03	-0.55 ± 0.05	0.997
CH ₃	-0.07	1.98 ± 0.02	-0.46 ± 0.02	0.998
H	0.00	1.96 ± 0.05	-0.46 ± 0.04	0.991
F	0.34	1.89 ± 0.03	0.12 ± 0.03	0.998
Cl	0.37	1.79 ± 0.04	0.22 ± 0.08	0.991
CN	0.56	1.86 ± 0.04	0.33 ± 0.07	0.993
NO ₂	0.71	1.90 ± 0.04	0.76 ± 0.06	0.995

^aSolvent = toluene, temperature = 25°. ^bReference 5.

Table III. Temperature Dependence of β_2 for Two Para-Substituted NiTPP Complexes

Para substituent	Temp, °C	n	Log β_2	ΔH , kcal/mol	ΔS , eu
H	22.0	1.94 ± 0.03	-0.37 ± 0.03	-5.6 ± 0.5	-21 ± 2
	25.0	1.96 ± 0.05	-0.46 ± 0.04		
	30.0	1.92 ± 0.05	-0.54 ± 0.04		
	35.0	2.03 ± 0.06	-0.62 ± 0.08		
	45.2	1.95 ± 0.07	-0.70 ± 0.10		
CN	22.0	1.97 ± 0.05	0.56 ± 0.06	-8.7 ± 1.1	-27 ± 4
	25.0	1.67 ± 0.17	0.41 ± 0.19		
	35.3	1.83 ± 0.13	0.27 ± 0.11		
	45.1	1.78 ± 0.15	0.06 ± 0.12		

Table IV. Equilibrium Constants for Addition of Piperidine to VO(*p*-X)TPP ($\rho^{\text{V}} = 0.113 \pm 0.003$)

Para substituent	Temp, °C	σ_X^a	Log K_1^V	ΔH , kcal/mol	ΔS , eu
OCH ₃	25.0	-0.268	-0.44 ± 0.07	-5.6 ± 0.4	-21 ± 1
	34.5	-0.170	-0.42 ± 0.04		
	45.3		-0.55 ± 0.06		
			-0.68 ± 0.07		
H	25.0	0.000	-0.40 ± 0.05		
Cl	25.0	0.227	-0.28 ± 0.11		
CN	25.0	0.660	-0.17 ± 0.11		

^aReference 5.

same concentration of Ni(X)TPP in the presence of a large excess of piperidine, A_i is the absorbance of a solution containing an intermediate concentration of piperidine, and $[\text{Pip}] = [\text{Pip}]_0 \approx [\text{Pip}]_{\text{eq}}$. A plot of $\log(A_i - A_0)/(A_c - A_i)$ vs. $\log[\text{Pip}]$ is expected to give a slope of 2 and an intercept of $\log \beta_2$. Although, as discussed below, large concentrations of a monopiperidine complex were generally present, its visible spectrum was almost identical with that of the four-coordinate reactant, and thus spectral changes were indicative only of the overall addition of 2 mol of piperidine.

In Table I are listed, respectively, the values of $\log \beta_2$ for the reaction of piperidine with Ni(*p*-X)TPP at 22°, the number of moles of piperidine in each of the complexes de-

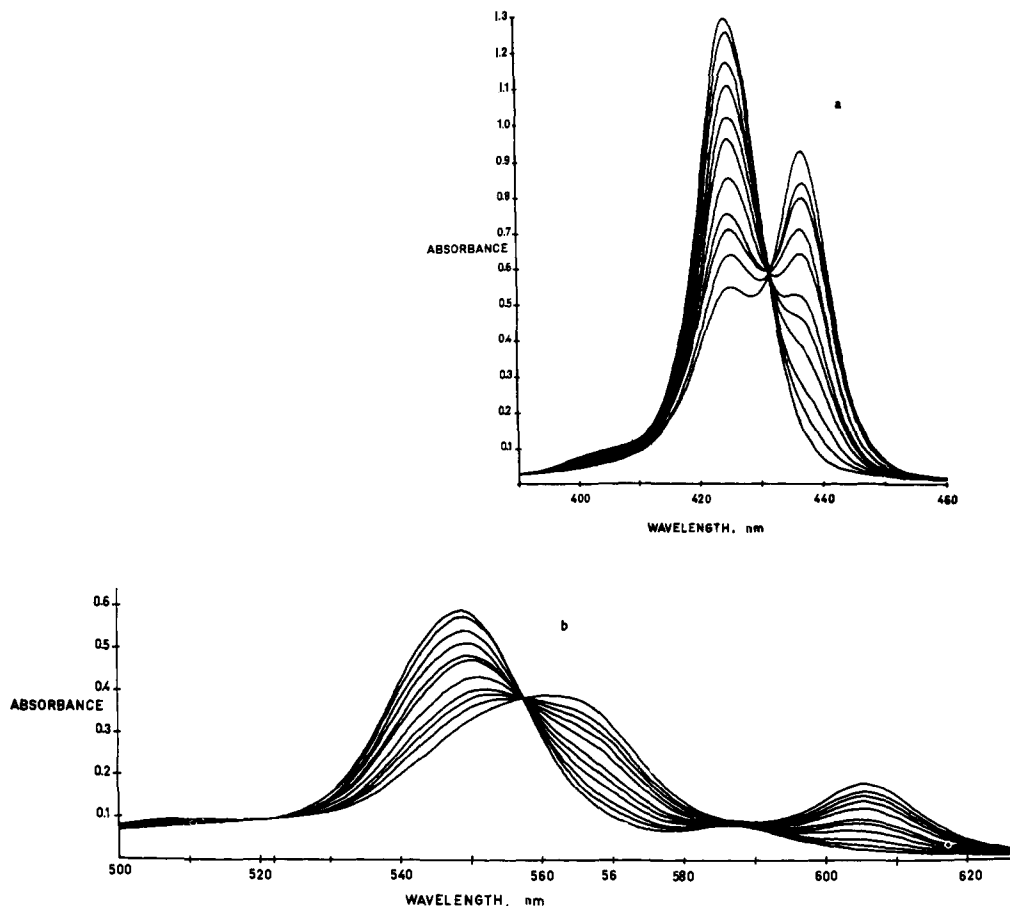


Figure 2. Visible spectra of VO(*p*-CH₃)TPP in the presence of varying amounts of piperidine. [VO(*p*-CH₃)TPP] = 2.65×10^{-5} M: (a) cell path length = 1 mm; (b) cell path length = 1 cm. Typical absorption maxima and extinction coefficients of the five- and six-coordinate complexes are given in the Experimental Section.

terminated from the least-squares slope of the log-log plot, and the σ constants for each of the substituents X. The same quantities for the reaction of piperidine with Ni(*m*-X)TPP at 25° are listed in Table II. Enthalpies and entropies for reaction 1, where X = H and *p*-CN, which were determined by measuring $\log \beta_2$ as a function of temperature, are listed in Table III.

Values of $\log K_1^V$ for reaction 3 and the σ constants for each of the substituents X are listed in Table IV, as are the derived values of ΔH and ΔS for the reaction of VO(*p*-CH₃)TPP with piperidine. Plots of $\log K_{1X}^V$ and $\log \beta_{2X}$ for Ni(*p*-X)TPP vs. $4\sigma_X$ (eq 2a) are shown in Figure 3.

The log-log plots for Ni(*p*-X)TPP and Ni(*m*-X)TP were linear and all gave slopes within or very close to experimental error of $n = 2.00$, as shown in Tables I-III. This indicates that at the wavelengths utilized in the calculation of β_2 , no evidence for the formation of a monopiperidine complex was obtained.

In dilute piperidine ($< 5 \times 10^{-2}$ M) it was possible to observe the formation of the monopiperidine adduct of NiTPP (eq 4) at 437.6 nm by the difference technique. A value of $K_1^{Ni} \sim 200 \pm 100$ M⁻¹ was estimated from spectra recorded at 22°. However, the accuracy and precision of this equilibrium constant is limited by the very small change in the absorbance at 437.6 nm ($\Delta\epsilon = 6.36 \times 10^2$), where NiTPP and NiTPP(Pip)₂ both absorb strongly ($\epsilon 1.92 \times 10^4$ and 1.41×10^5 , respectively). Thus, when [Pip] = 5×10^{-2} M, the small ($\sim 10^{-8}$ M) concentration of the bispiperidine complex present contributes to ΔA to the extent of about 10% of the measured value. Therefore, the value of $K_1^{Ni} = 200$ M⁻¹ must be regarded as only an estimate. Because of the minute change in the spectrum upon formation of the

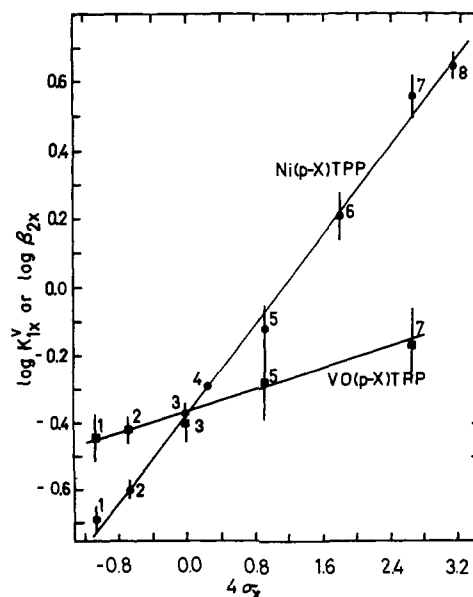


Figure 3. Plot of $\log \beta_{2X}$ and $\log K_1^V$ vs. σ_X : ● = Ni(*p*-X)TPP, ■ = VO(*p*-X)TPP. 1 = OCH₃, 2 = CH₃, 3 = H, 4 = F, 5 = Cl, 6 = COOCH₃, 7 = CN, 8 = NO₂.

monopiperidine complex (≤ 0.001 absorbance units under the conditions of measurement of $\log \beta_2$), the absorbances of the solutions used for measurement of $\log \beta_2$ were not sensitive to the presence of the monopiperidine complex, thus allowing reaction 1 to be investigated without correction for the concentration of the monopiperidine complex.

The ESR parameters of the VO(*p*-X)TPP and their piperidine adducts were equal, within experimental error, throughout the series of substituents X, and showed no relationship to the σ constants. The isotopic spectra were relatively sharp at 100°, and any overlap of hyperfine lines was minimized. For VOTPP, $|a_0| = 98.1 \pm 1.0$ G and $g_0 = 1.976 \pm 0.001$ in toluene and 96.6 ± 1.0 G, 1.978 ± 0.001 in piperidine. The mechanism of line broadening at lower temperatures is that of incomplete modulation of the g and hyperfine anisotropies due to slow rotation of these rather large molecules.¹⁷ The rotational correlation time, τ_c , has an inverse dependence on r^3 , where r is the average effective molecular radius.¹⁷ It was noted that the differences in effective radius r of the various VO(*p*-X)TPP complexes (dependent upon the size of the para substituent) were clearly manifest in the widths of the eight hyperfine lines.¹⁸ In frozen toluene glass, VOTPP gave $|A_{||}| = 174.3 \pm 1.0$ G, $|A_{\perp}| = 61.9 \pm 2.0$ G, $g_{||} = 1.962 \pm 0.001$, and $g_{\perp} = 1.985 \pm 0.002$, and, in frozen piperidine, $|A_{||}| = 170.9 \pm 1.0$ G, $|A_{\perp}| = 59.4 \pm 2.0$ G, $g_{||} = 1.965 \pm 0.001$, and $g_{\perp} = 1.985 \pm 0.002$.

Discussion

Reaction 1. Formation of Ni(*m*- or *p*-X)TPP(Pip)₂. The data of Tables I and II and Figure 3 clearly show that β_2 is strongly dependent on electron withdrawing or donating characteristics of substituents as far distant as the meta and para positions of the phenyl rings of a series of substituted tetraphenylporphyrin complexes. For para substituents, X is at a distance of about 9 Å and seven bonds from the metal atom, and yet the slope of the plot of Figure 3, for M = Ni, para substituents, gave $\rho^{\text{Ni(p)}}$ = 0.331 ± 0.005, while a plot of the log β_2 values for the meta series (not shown) gave $\rho^{\text{Ni(m)}}$ = 0.413 ± 0.06. The existence of such a Hammett relationship is somewhat remarkable, in view of the fact that X-ray crystallographic structure determinations of metallotetraphenylporphyrin complexes invariably show¹⁹ that the phenyl rings are not in the plane of the porphyrin and thus cannot be fully conjugated with the porphyrin ring. Space-filling molecular models (Corey, Pauling, Koltun) show that steric interference between the ortho-H of the phenyl ring and the pyrrole-H of the tetraphenylporphyrin acts to prevent coplanarity of the rings. The barrier to rotation of the phenyl rings has been estimated as ≥17 kcal/mol.^{20,21}

However, even though coplanarity of the rings of tetraphenylporphyrin is prevented by steric interference, significant overlap of π systems has previously been suggested from ir,²² ESR,²³ and NMR^{21,24} studies of metallotetraphenylporphyrins. It may be anticipated that if the substituents, X, were attached directly to the meso positions rather than at the para positions of meso-phenyl groups, the sensitivity of reaction 1 to electronic effects would be considerably greater than observed here. A plot of the values of log $\beta_2(25^\circ)$ for deuteroporphyrin complexes of Ni(II) in which the 2,4-substituents are C₂H₅, H, and COCH₃^{4a} yields a value of $\rho = 1.4$ in this unsymmetrical porphyrin system. Thus, in this crude comparison, it would appear that a substituent on the para position of a phenyl ring in tetraphenylporphyrin complexes has an effect approximately one-quarter that of a substituent attached directly at the pyrrole position of a 2,4-disubstituted deuteroporphyrin as far as the addition of ligands to Ni(II) porphyrins is concerned.

In comparing the electronic effects of 2,4-disubstituted deuteroporphyrins^{4a} to para-substituted tetraphenylporphyrins in terms of reaction 1, it would appear that 2,4-diacetyldeuteroporphyrin IX is similar to (*p*-F)TPP, and 2,4-diformyldeuteroporphyrin IX is similar to (*p*-COOCH₃)TPP, if there were no major differences in the solvent employed.

However, because of hydrogen bonding between piperidine and chloroform, the apparent equilibrium constants measured by McLees and Caughey^{4a} are probably smaller than those which could be measured in toluene solution.

The ΔH values for addition of two molecules of piperidine to NiTPP and Ni(*p*-CN)TPP are negative and relatively small, due to the unfavorable enthalpy associated with the spin change ($S = 0 \rightarrow S = 1$). The six-coordinate product thus has an unpaired electron in the d_{z^2} orbital, as well as one in the $d_{x^2-y^2}$ orbital, both antibonding with respect to the lone pairs of the bases. The presence of these two antibonding electrons increases both the length of the Ni-N(pip) and the Ni-N(porph) bonds²⁵ over those of the d^6 CoTPP(Pip)₂⁺ complex.^{19f}

Derived values of ΔS for reaction 1 (Table III) are negative and within the range generally expected (−20 to −30 eu) for addition of two ligands to a metal complex. Because of the similar structures of the series of Ni(*m*- or *p*-X)TPP complexes, all compounds are expected to be similarly solvated in toluene solution, and changes in solvation upon complex formation should also be similar throughout the series of compounds studied. Thus the values of $\Delta S = -21$ (X = H) and -27 eu (X = CN) are indicative of a similar solvation contribution to the stability of the complexes formed with piperidine. This means that log β_2 is almost directly proportional to ΔH , as one would expect to be generally true of a series of compounds of such closely related structures. The same comparison of ΔH and/or ΔS values for reaction 1 among a series of 2,4-disubstituted deuteroporphyrins^{4a} is not so easily made because of the major structural differences, which are expected to cause major differences in solvation and aggregation¹⁴ in this series of compounds, and thus a solvation term of unknown and variable magnitude is contributed to each ΔH and ΔS .

Reaction 3. Formation of VO(*p*-X)TPP(Pip). In contrast to the Ni(II) case, the data of Table IV and Figure 3 clearly show that log K_1^V is much less dependent on the electron withdrawing or donating characteristics of substituents on the phenyl rings. The slope of the plot of Figure 3, M = VO²⁺, is $\rho^V = 0.113 \pm 0.002$, or about one-third those for the Ni(II) reactions.

An investigation of the reaction of pyridine with a series of modified natural porphyrin V(IV) complexes in chloroform solution gave $\rho \sim 0.65$,^{26,27} approximately six times that of the present study of the para-substituted tetraphenylporphyrins. The equilibrium constants measured were in general smaller than those of the present study.

One major difference between the Ni(II) and V(IV) complexes may be that the V(IV) atom is thought to be 0.5–0.8 Å above the plane of the porphyrin ring, on the basis of theoretical calculations,²⁸ and one X-ray crystallographic structure determination of a natural V(IV) porphyrin has shown the V atom 0.48 Å out of the plane, while the four-coordinate Ni(II) porphyrins have the nickel atom in the plane. An out-of-plane position of the metal atom could change the overlap between vanadium π -symmetry d orbitals and the porphyrin π and π^* orbitals, and thus possibly decrease the sensitivity of the vanadium atom to substituents, as has been suggested by Hambricht.³⁰ However, the geometry of the five-coordinate monopiperidine intermediate in the Ni(II) case is not known, and it may show similar out-of-plane displacement to that of the V(IV) atom.

Another difference between the Ni(II) and V(IV) complexes is the number of d electrons on the metal: eight as compared to one. More important, of the eight electrons of Ni(II), four (the maximum possible) are in orbitals of proper symmetry for d_{π} back-bonding interactions with the π^* orbitals of the porphyrin (M → L π back-bonding). In the case of V(IV), the lone d electron is in the d_{xy} orbital,³¹ and

cannot interact with the π^* orbitals of the porphyrin ring. The empty d_{xz} and d_{yz} orbitals of V(IV), however, have proper symmetry for overlap with filled π orbitals of the porphyrin ring ($L \rightarrow M \pi$ back-bonding). However, these filled π orbitals are probably at considerably lower energy than the d orbitals of the vanadium ion. If such overlap is favorable, more electron density would be placed on vanadium when an electron donating substituent is present on the phenyl groups than when an electron withdrawing substituent is present.

As complexes are formed with additional ligands, electron density builds up on the metal. If this electron density may be partially dissipated by delocalization onto the porphyrin ring through $d_{\pi}-\pi^*$ back-bonding, as in the case of Ni(II), then the formation of complexes with additional ligands will be more favorable. If the ligand is able to withdraw electron density from the porphyrin ring, as, for example, in the cases $X = \text{NO}_2, \text{CN}, \dots$, then the formation of complexes with additional ligands should be even more favorable. If the porphyrin ligand is already acting as a π donor to the metal, as is the only possible π interaction for the V(IV) case, then this buildup of electron density on the metal should make complex formation more unfavorable as the amount of electron density donated increases, or as the σ constant of X becomes less positive. Although the experimental facts are not in disagreement with this interpretation, the magnitude of ρ^V is much smaller than those of $\rho^{\text{Ni}(p)}$ and $\rho^{\text{Ni}(m)}$. Thus it would appear that if $L \rightarrow M \pi$ back-bonding is involved in this case, it must be a less important means of electron delocalization in metalloporphyrins than $M \rightarrow L \pi$ back-bonding. Further studies of other M(X)TPP systems are in progress to test this hypothesis.

The ΔH for addition of piperidine to $\text{VO}(p\text{-CH}_3)\text{TPP}$ is small and negative, and the ΔS for reaction 3 is somewhat more negative than generally expected for addition of one amine molecule to a metal complex. This may reflect more rigidity in and lack of internal rotation about the vanadium-piperidine bond in the porphyrin complex than in vanadium(IV) complexes with bidentate ligands.³² The small ΔH value as well as the small values of K_1^V in comparison to K_1 values for addition of ligands to other V(IV) complexes³² indicate the extreme dominance of the bonding and structure by the porphyrin ring. The similarity of ΔH and ΔS values for the Ni(II) and V(IV) porphyrin reactions (Tables III and IV) despite the difference in stoichiometry of the reactions probably arises from a combination of the above-mentioned rigidity in the V(IV) system and an unfavorable contribution to the enthalpy in the Ni(II) reaction due to the spin change.

The lack of any significant dependence of the ESR parameters on the substituent X is not surprising in view of the small sensitivity of the equilibrium constant for reaction 3. Although it was found, for a series of substituted natural porphyrin complexes of Cu(II), that g_{\perp} was linearly related to the Hammett σ constants of substituents,⁵ variation of g_{\perp} is extremely small throughout the series of complexes investigated, as would be expected if π electron delocalization is most important in these natural porphyrins, since the electron is in the copper $d_{x^2-y^2}$ orbital, σ antibonding in nature.

Inductive and Resonance Contributions to Log β_2 and Log K_1^V . The question of the degree of conjugation of the π systems of the phenyl rings with the porphine ring has been raised by a number of investigations. X-Ray structure determinations of metallotetraphenylporphyrins have generally shown that the phenyl rings are at nearly 90° angles to the porphine plane.¹⁹ Chlorine superhyperfine splittings have been observed in the ESR spectrum of $\text{Cu}(p\text{-Cl})\text{TPP}$ in frozen glasses,²³ and π unpaired electron delocalization

to the ortho and para protons of the phenyl rings of FeTPP and the corresponding *o*-, *m*-, and *p*- CH_3 substituted porphyrin complexes has been found in NMR investigations of these high spin hemins in deuteriochloroform solution.^{21,24} The best fit between calculated and experimental dipolar shifts of the corresponding low spin hemins was obtained if the phenyl rings were allowed an oscillation slightly greater than 30° from the normal to the porphine plane.³⁴ However, in an investigation of the Mossbauer spectra of a series of high spin hemin derivatives of para-substituted tetraphenylporphyrins, it was assumed that the aryl groups were not in conjugation with the porphine ring.³⁵ Indeed, no correlation between Hammett σ constants and either isomer shift or quadrupole splitting was observed in this system. This may be due to the fact that, as suggested by the authors, Mossbauer parameters may be more dependent upon crystal packing phenomena caused by substituents than upon the electronic effects of these substituents.

In an attempt to quantify the importance of direct conjugation or π overlap in the transmission of substituent effects in metallotetraphenylporphyrins, we have applied the dual substituent parameter analysis of Taft and coworkers^{36,37} to this system. Their dual parameter equation is

$$P^i = \sigma_I \rho_I^i + \sigma_R \rho_R^i \quad (8)$$

where P^i is the substituent effect from the i th position, σ_I is the σ constant characteristic of inductive (polar) effects, and σ_R is one characteristic of resonance (π delocalization) effects. The ρ_I^i and ρ_R^i values represent the sensitivity of the reaction in question to inductive and resonance effects of substituents in the i th position. They have defined four types of σ_R scales,³⁶ three of which are potentially applicable to the equilibria of complex formation between amines and metalloporphyrins.

(a) σ_R^0 constants are valid for systems in which there is little or no significant through-conjugation between substituent and reaction center. Transmission of electronic effects of substituent X to the reaction center is mainly by field and internal π induction.

(b) $\sigma_R(\text{BA})$ constants are applicable in general to systems which involve only very moderate direct conjugation between the substituent X and the reaction center.

(c) σ_R^+ constants are applicable to systems in which there is strong direct conjugation between X and the electron deficient or positively charged reaction center.

The least-squares ρ_I and ρ_R values for the three systems of interest in this investigation, calculated from eq 8 using each set of σ_R constants (where each σ constant has been multiplied by 4 to take into account the presence of four equivalent substituents) are listed in Table V, along with the standard deviation, SD, for the fit between measured and calculated $\log K_1^V$ or $\log \beta_2$. Unfortunately, the data do not discriminate as clearly as might have been hoped among the three possible types of resonance interaction between X and the metal, since the error in $\log K_1^V$ or $\log \beta_2$ (Tables I, II, and IV) is in general considerably larger than the standard deviations of the best fits (0.01, 0.02). It is interesting to note, however, that, as substituent constant scales which imply increasingly direct conjugation between X and metal are utilized, ρ_R becomes progressively smaller in all three metalloporphyrin systems investigated so far (compare ρ_R^0 , $\rho_R(\text{BA})$, and ρ_R^+ in Table V). On the basis of this, the larger standard deviation, and on structural grounds discussed above, it is reasonable to eliminate the possibility of full conjugation (case c, ρ_R^+) between X and metal. However, a clear distinction between field and internal π induction (case a, ρ_R^0) and moderate direct conjugation (case b, $\rho_R(\text{BA})$) cannot be made in the present case.

Table V. Separation of Substituent Effects into Inductive and Resonance Contributions^a

System	Case a Field and π induction			Case b Moderate conjugation			Case c Direct conjugation		
	ρ_I	ρ_R^0	SD ^e	ρ_I	$\rho_R(\text{BA})$	SD ^e	ρ_I	ρ_R^+	SD ^e
Ni(<i>p</i> -X)TPP + 2 Pip ^b	0.315	0.375	0.02	0.330	0.300	0.04	0.320	0.203	0.08
Ni(<i>m</i> -X)TPP + 2 Pip ^c	0.378	0.200	0.13	0.380	0.168	0.11	0.375	0.118	0.11
VO(<i>p</i> -X)TPP + Pip ^d	0.085	0.073	0.01	0.085	0.060	0.01	0.085	0.038	0.01

^a σ_I and σ_R values used in least-squares calculations of ρ_I and ρ_R are taken from ref 31. ^b Log β_2 used in least-squares calculation of ρ_I and ρ_R taken from Table I. ^c Log β_2 used in least-squares calculation of ρ_I and ρ_R taken from Table II. ^d Log K_1^V used in least-squares calculation of ρ_I and ρ_R taken from Table IV. ^e Standard deviation for agreement between experimental and calculated values of log β_2 or log K_1^V .

Taft and coworkers have noted that some systems give an indiscriminate fit to either scale.³⁷

Either of these types of π electron effects could presumably account for the magnetic resonance observations noted previously for other metalloporphyrin systems,^{21,23,24,34} and whether moderate conjugation or π induction is the mechanism of resonance effect of the substituent, *the resonance and inductive contributions to the observed substituent effects* (Figure 3) *are of similar magnitude in the two para-substituted systems*, while in the Ni(*m*-X)TPP system, resonance effects are about half as important as inductive effects, and inductive effects are more important in the Ni(*m*-X)TPP system than in the Ni(*p*-X)TPP system, both of which are expected for a well-behaved system.³⁶

Reaction 4. Formation of NiTPP(Pip). A recent study of the addition of one molecule of base to NiTPP, where the base was one of a series of substituted pyridines has been reported.³³ In benzene solution typical K_1^{Ni} values are 1414 (pyridine) and 720 M^{-1} (4-CN pyridine). No obvious relationship between ligand basicity and K_1^{Ni} was observed in benzene or chloroform. The method of investigation was the same as that of the present study of reaction 4. The value of K_1^{Ni} estimated in this study, 200 M^{-1} in toluene solution at 22°, is similar in magnitude to those reported previously.³³ Measurement of ΔH was not attempted in the present investigation because of the large interference of the bispiperidine complex formation on the interpretation of difference spectra, and we question the validity of thermodynamic quantities determined for systems in which such minute changes in spectra take place.

The reported differences in stoichiometry (1:1³⁸⁻³⁹ or 1:2^{40,41}) of Ni(II) porphyrin complexes with axial bases arise in part (a) from differences in the basicity of the amine chosen (pyridine and substituted pyridines generally form predominantly 1:1 complexes,³⁸ while piperidine also forms 1:2 complexes at high base concentrations,⁴⁰ and *N*-methylimidazole appears to form a mixture of 1:1 and 1:2 species¹⁸) and (b) from differences in the solvent chosen. A commonly used solvent is chloroform,^{4,39} which is well known to hydrogen bond extensively to basic solutes such as amines. Thus the concentration of free amine available for complex formation is much lower than assumed, particularly in the case of piperidine, and the calculated number of ligands involved in complex formation in some studies falls considerably below the value of 2.0 consistently found in this work. Since metallotetraphenylporphyrins generally form less thermodynamically stable axial adducts than their natural porphyrin analogs, it is unlikely that piperidine forms solely a 1:1 complex with an Ni(II) porphyrin investigated to date.

Stepwise addition of two imidazoles to a water-soluble Ni(II) porphyrin has been reported,⁴² but in this case it appears that coordinated water molecules are replaced by the imidazole molecules, and there is no direct evidence of a five-coordinate intermediate.

The electronic spectral and spin changes which accompany mono- and bispiperidine complex formation by Ni(X)TPP are of interest. An almost imperceptible change in the electronic spectrum is observed on going from four- to five-coordination in toluene solution, but a dramatic change takes place upon going from five- to six-coordination. No theoretical calculations have been reported on the spectral changes of Ni(II) porphyrins upon change of coordination number, but such calculations would be of interest. The spin change, from $S = 0$ to $S = 1$, appears to take place during the second step of ligand addition, as shown by NMR techniques.⁴³ However, the NMR study has also provided evidence of either a spin equilibrium or a low energy $S = 1$ excited state for the five-coordinate monopiperidine complex. It would be tempting to correlate major changes in the electronic spectrum of Ni(X)TPP with the change in spin state if it were not for the fact that VO(*p*-X)TPP complexes also undergo similar major spectral changes upon complex formation, and here no change in spin state is involved.

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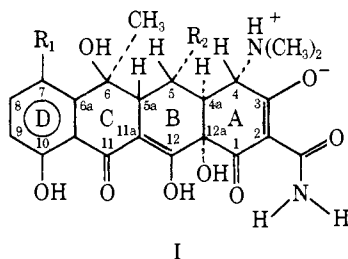
A Proton Nuclear Magnetic Resonance Study of the Site of Metal Binding in Tetracycline

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Abstract: An investigation directed toward establishing the site(s) of metal binding in the antibiotic tetracycline has been carried out in DMSO-*d*₆ solution using proton NMR. The paramagnetic ions Nd(III), Tb(III), V(III), Cu(II), Mn(II), and Co(II) and the diamagnetic ions La(III), Ca(II), and Mg(II) have been used. Isotropic shifts and broadening of certain tetracycline ¹H NMR signals are observed in the presence of paramagnetic ions. Diamagnetic ions also affect some of these ¹H NMR signals. Analysis of the selective effects of these ions on the ¹H NMR signals has led to the conclusion that in DMSO solution metal binding occurs at the tricarbonylmethane function of ring A, probably through oxygen donors.

The tetracyclines are a family of broad-spectrum antibiotics used extensively by the medical profession for more than 2 decades. The structures of 7-chlorotetracycline (Aureomycin; I, R₁ = Cl, R₂ = H) and 5-hydroxytetracycline (Terramycin; I, R₁ = H, R₂ = OH) were first deduced from chemical experiments and later confirmed through X-ray crystallographic studies. A review of the structural work and reaction chemistry of tetracyclines appeared in 1968.²



The multiplicity of potential metal binding sites present in the tetracyclines has attracted much interest. Albert^{3,4} measured stability constants of metal complexes of these antibiotics in the early 1950's. The stability constants found for a number of metal ions are of the same order as those for β -diketonate or α -aminoacidate complexes of these ions,⁵ and Albert recognized that tetracyclines must compete for metal ions in the human body. Concurrently it was discovered that the presence of excess metal ions neutralizes the effects of tetracyclines.^{6,7} A series of experiments by

Doluisio and Martin showed that therapeutically active tetracyclines form 2:1 ligand-to-metal complexes with Cu²⁺, Ni²⁺, and Zn²⁺, whereas certain therapeutically inactive derivatives form only 1:1 complexes with these ions.⁸ Also, using metal-free conalbumin as a model metalloenzyme drug receptor, they found binding of active tetracyclines to the receptor is greatly enhanced in the presence of Cu²⁺, suggesting the existence of ternary drug-metal-receptor complexes.⁹ Acting on the hypothesis that tetracyclines act by uncoupling oxidative phosphorylation through inhibition of metalloflavoenzymes, Colaizzi and coworkers measured the extent of inhibition of the metalloflavoenzyme NADH-cytochrome *c* oxidoreductase by a series of therapeutically active and inactive tetracyclines.¹⁰ They presented evidence that inhibition results from chelation of iron in the enzyme by the drugs and suggested that the mode of action of tetracycline antibiotics involves inhibition of bacterial metalloflavoenzymes by chelation of enzymatically bound metal.

It is now generally agreed that the ultimate effect of tetracycline antibiotics in minimum doses is inhibition of bacterial protein synthesis as a result of binding of the drugs to bacterial ribosomes,¹¹⁻²¹ possibly mediated by metal ions such as magnesium.^{11,13-16,18-21} It has also been proposed that metal ions serve to neutralize the charge on tetracyclines, thus enhancing transport through lipophilic bacterial cell walls.²² There is some evidence that membrane penetration by tetracycline involves reversible association of the drug with membrane-associated cations, since chelating agents such as EDTA and ATP have marked inhibitory effects on uptake of tetracycline by membranes.²³ Although