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Metal-assisted template syntheses of 5,10,15,20-tetraalkylchlorin and tetraalkylporphyrin complexes of transition metals are described. With Co only the porphyrins are obtained; with Cu only the chlorins; with Ni a mixture of chlorin and porphyrin is obtained depending on alkyl and added anhydride. As opposed to the higher alkyls, (5,10,15,20-tetramethylporphyrinato)nickel(II) dimerizes in solution, a dimerization constant of $3.9 \pm 1.3 M^{-1}$ being derived from 1H nmr data.

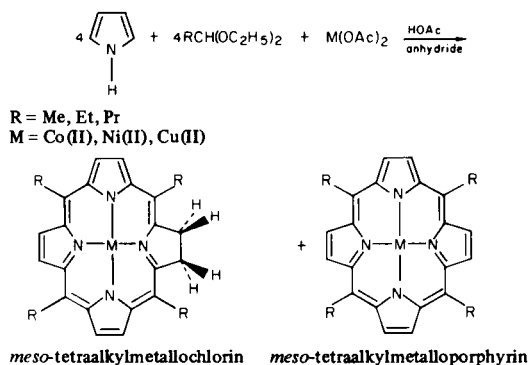
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Introduction.

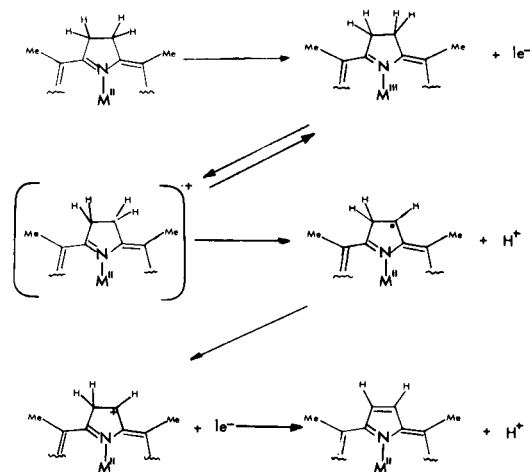
The modeling of coordination sites in metallobiomolecules contributes increasingly to our understanding of the properties of such molecules (1) and is of central importance in the study of porphyrin-containing proteins (2). For such modeling, except where elaboration of the skeleton is required to control reactivity, the porphyrins of choice, dictated essentially by ease of preparation, have been 5,10,15,20-tetraphenylporphyrin (TPP) and 2,3,7,8,12,13,17,18-octaethylporphyrin (OEP). We sought a simpler porphyrin system that would offer the following advantages: (i) elimination of conjugation of the porphyrin core and of potential cation radicals with other aromatic systems, such as phenyl substituents; (ii) minimization of possible disorder in the solid state, as, for example, occurs with some octaethyl derivatives (3); (iii) increased simplicity for bonding electron density determinations and ensuing theoretical calculations. In addition, since it is now clear that chlorins are of biological importance (1,4), we sought a synthesis of an analogous chlorin system that would be free from isomeric contamination. For these reasons we turned our attention to the synthesis of 5,10,15,20-tetramethylporphyrin (TMP), the analogous chlorin (TMC), and related tetraalkyl systems.

Two basic strategies may be used for the synthesis of chlorins: (i) synthesis of the appropriate porphyrin, followed by reduction or (ii) direct synthesis. Because of the

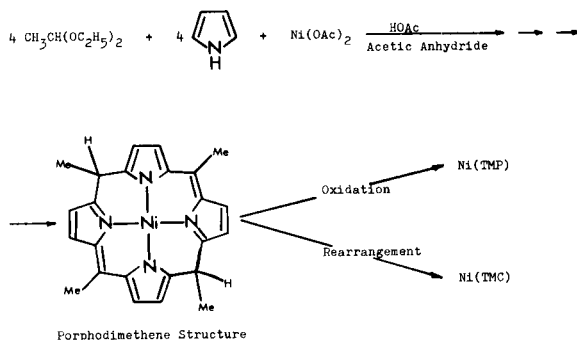
Scheme 1



Scheme 2



Scheme 3



ready availability of TPP and OEP derivatives, the chlorin analogues, TPC and OEC, are generally produced by reduction (5). However, for the synthesis of TMC the difficulties in the synthesis of TMP make this approach less desirable. Maltzan (6) reported a synthesis of Ni(TMP) in 4.3% yield. Tabushi, *et al.*, (7) have reported the synthesis of H₂TMP in 8.7% isolated yield (8). The first direct synthesis of TMC was by Eisner (9), who used the Mannich base approach. The synthesis was complicated by problems of isolation and purification.

In all of the suggested syntheses of porphyrins there are

Table I

	Soret, λ max nm ($\epsilon \times 10^{-4}$)		Q - Bands, λ max nm ($\epsilon \times 10^{-3}$)			
H ₂ TMP (a)	370-75 (2.14)	420 (28.2)	522 (12.3)	577 (8.95)	605.5 (3.7)	657.5 (6.8)
		489 (3.5)				
H ₂ TMP ²⁺ (a)		417.5 (29.2)	544 (2.6)	582 (6.9)	630 (18.0)	
Ni(TMP)		418 (19.3)	502 (3.1)	537 (12.2)	570 (2.5)	
Cu(TMP) (a)		420 (37.0)	549 (12.6)	587.5 (4.2)		
Ni(TEP)		417 (18.9)	501 (2.9)	536 (11.5)	572 (2.7)	
Ni(TPrP)		418 (29.9)	502 (4.3)	537 (18.6)	570 (4.0)	
H ₂ TMC (a)	372.5 (3.1)	411 (11.3)	532.5 (11.4)	577 (10.3)	602.5 (5.3)	656 (20.4)
		437 (78.3)				
H ₂ TMC ²⁺ (a)		421 (12.0)	545 (3.6)	587 (5.8)	635 (19.0)	
		442 (70.6)				
Ni(TMC)		421 (15.2)	510 (3.94)	583 (10.1)	618 (23.1)	
Cu(TMC) (a)		419 (14.9)	519 (4.0)	587 (8.6)	618 (20.1)	

(a) From reference 9.

reports of "contamination" by chlorins (10), and purification procedures have been established to obtain pure porphyrins (11). For TMP, as opposed to TPP and OEP, contamination appears to be more serious, necessitating long air oxidations. It is probable that TMC has a higher oxidation potential than TPC or OEC. Template syntheses of metalloporphyrins are well known (*e.g.*, (tetrabenzoporphyrinato)zinc(II) (12)), and since the oxidation potentials of metalloporphyrins to yield π -cation radicals are higher than those of the corresponding free bases, we expected that the use of template syntheses might, on the one hand, increase this "contamination" to the point where the synthesis of a metallochlorin was efficient and, on the other hand, through appropriate change of metal might enable us to eliminate the contamination of por-

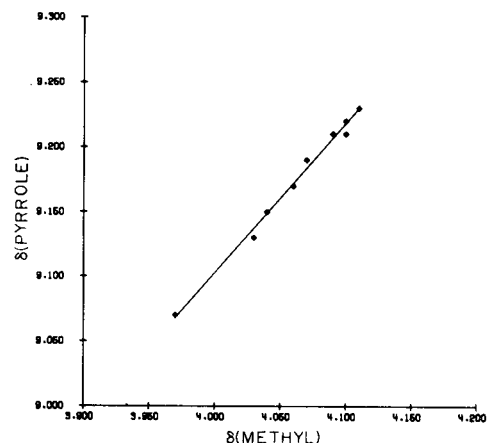


Figure 2. A plot of δ (H, pyrrole) vs δ (H, methyl) as a function of [Ni(TMP)].

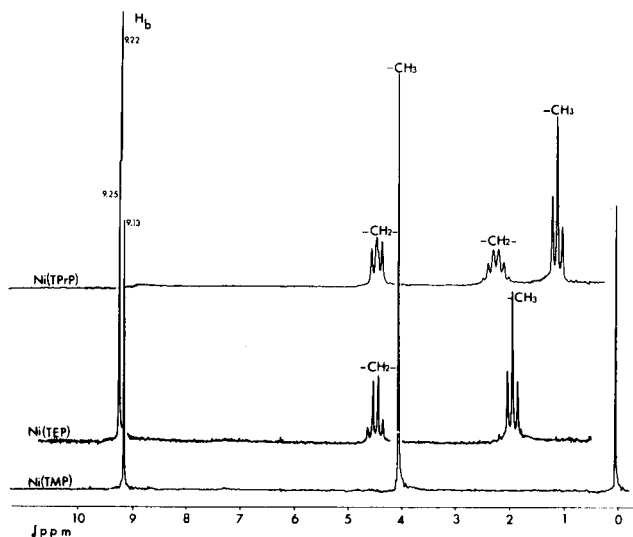


Figure 1. ¹H nmr spectra (80 MHz) of Ni(TMP), Ni(TEP), and Ni(TPrP) in deuteriochloroform.

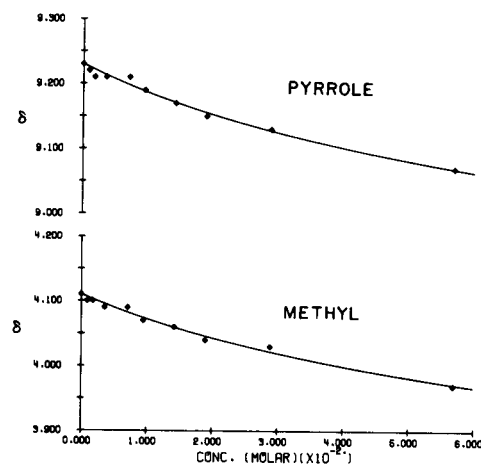


Figure 3. Observed vs calculated chemical shifts for the pyrrole and methyl protons of Ni(TMP) as a function of [Ni(TMP)].

phyrin by chlorin. In this paper we report the details of our successful syntheses.

Results and Discussion.

The reaction of acetal with pyrrole in the presence of nickel acetate and 2% acetic anhydride (Scheme 1, $M = Ni$, $R = Me$) affords a mixture of Ni(TMP) and Ni(TMC) in a 1:4 molar ratio. The reaction is completed in a few hours, and the only products, Ni(TMP) and Ni(TMC), are readily separated chromatographically. The isolated yields are comparable with those obtained by more laborious procedures.

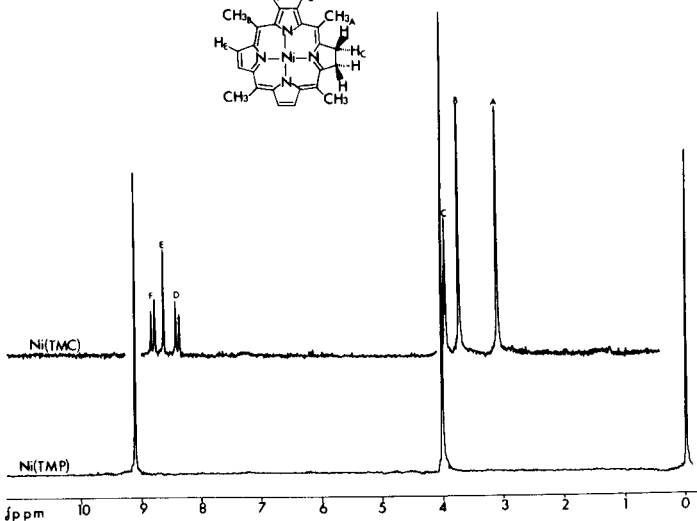
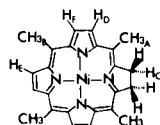


Figure 4. 1H nmr spectra (80 MHz) of Ni(TMP) and Ni(TMC) in deuteriochloroform.

Table II

Chemical Shifts in the 1H nmr Spectra of 5,10,15,20-Tetraalkylporphyrin and Chlorin Complexes of Ni(II)

Compound	Pyrrole	Pyrroline ring	Alkyl
Ni(TMP)	9.23 (s), 8H		4.11 (s), 12H
Ni(TEP)	9.25 (s), 8H		4.49 (d), J 7.5 Hz, 8H, 1.91 (t), J 7.5 Hz, 15H
Ni(TPrP)	9.22 (s), 8H		4.43 (t), J 8 Hz, 8H, 2.22 (m), J 8 Hz, 8H 1.08 (t), J 7.5 Hz, 12H
Ni(TMC)	8.83 (d), J 5 Hz, 2H 8.65 (s), 2H 8.43 (d) J 5 Hz, 2H	3.97 (s), 4H	3.73 (s), 6H; 3.08 (s), 6H

The chlorin/porphyrin ratio is strongly dependent on metal, added anhydride, and alkyl. When the reaction is carried out with cupric acetate (Scheme 1, $M = Cu$, $R = Me$), Cu(TMC) is the sole product. When instead the reaction is carried out with cobaltous acetate, Co(TMP) is the

sole product. These results are consistent with the known oxidation routes (ligand *vs.* metal) of M(TPP) systems (13) and suggest that oxidation of metallochlorin to metalloporphyrin may be catalyzed by metal oxidation and intra-electron transfer to give a π -cation radical, which by proton abstraction yields the porphyrin (Scheme 2). In porphyrin syntheses addition of anhydride to the acid reaction mixture decreases polymerization, enhances formation of a cyclic product, and increases yields (14). In Scheme 1 ($M = Ni$, $R = Me$) increasing the acetic anhydride concentration to 5% results in the production of pure Ni(TMC). This, along with the effect of different metals, suggests that chlorin formation is not a product of porphyrin reduction, being formed by rearrangement of a possible porphodimethene intermediate, rather than a direct product of the reaction (Scheme 3). Thus the mechanism here may differ from that suggested by Dolphin (15) for TPP. The reactions with higher acetals (Scheme 1, $R = Et$, Pr) give different ratios of products. For $M = Ni$ and 2% anhydride, only traces of Ni(TEC) can be detected, and with $R = Pr$, Ni(TPrP) is the sole product. Steric interactions have been shown to affect the products of porphyrin syntheses. For example, when 3,4-dimethylpyrrole reacts with benzaldehyde, intermediates such as porphyrinogen and porphodimethene can be isolated (15). This is believed to result from the steric interactions between the phenyl and methyl groups which slow the oxidation of the intermediates to porphyrins. In the present instance, inspection of models indicates that steric interaction is less effective in the oxidized form than in the reduced form, simply because there are two instead of four hydrogen atoms on the pyrrole of interest.

Table I summarizes the electronic spectra of some of the chlorin and porphyrin derivatives synthesized here. Spectral results from related systems are also tabulated.

Figure 1 displays 1H nmr spectra of Ni(TMP), Ni(TEP), and Ni(TPrP). Table II presents the chemical shift data. The position of the pyrrole proton in Table II and Figure

Table III

1H nmr Spectrum of Ni(TMP) as a Function of Concentration

[Ni(TMP)]	δ (pyrrole)	δ (methyl)	δ (CHCl ₃) (a)
0.0568	9.03 ppm	3.93 ppm	7.21 ppm
0.0284	9.11	4.01	7.23
0.0190	9.14	4.03	7.24
0.0142	9.16	4.05	7.24
0.0095	9.18	4.06	7.24
0.0071	9.20	4.08	7.24
0.0036	9.21	4.09	7.25
0.0018	9.21	4.10	7.25
0.0009	9.22	4.10	7.25
monomer (b)	9.23	4.11	

(a) This is the shift of the chloroform impurity in the deuteriochloroform solvent.

(b) Obtained by the addition of piperidine to a dilute solution.

Table IV

Parameter	Least-Squares Results for the Monomer-Dimer Equilibrium in Ni(TMP)	
	Pyrrole	Methyl
K (M ⁻¹)	3.9(1.3) (a)	3.0(0.7) (b)
Δδ (ppm)	0.64(14) (a)	0.94(15) (b)

(a) These values include an approximate correction (17) for the random averaging of the porphyrin ring current as derived from the δ (chloroform) values of Table IV. This is probably an over-correction.

(b) These values do not include such a correction.

1 differs for Ni(TMP) because its spectrum is concentration dependent (Table III). Spectra of Ni(TEP) and Ni(TPrP) are essentially independent of concentration in the range 0-0.06 M. Concentration dependent nmr spectra of porphyrins have been well-studied (16-18) and the present analysis is patterned after that of Abraham, *et al.*, (17) who explained the concentration dependence in terms of a monomer-dimer equilibrium, the dimer having different ring currents as a result of its parallel porphyrin components. In the present instance a plot of δ (H, pyrrole) vs δ (H, methyl) yields a straight line (Figure 2) as expected if these shifts arise from the same effect, such a monomer-dimer equilibrium. The observed chemical shift, $\Delta\delta_{\text{obs}}$, at any concentration, c , is given by:

$$\Delta\delta_{\text{obs}} = \delta_{\text{obs}} - \delta_{\text{monomer}} = \Delta\delta(1 + 8cK)^{1/2} - 1^2/(8cK) \quad (1)$$

where K is the equilibrium constant of dimerization and $\Delta\delta = \delta_{\text{dimer}} - \delta_{\text{monomer}}$, the complexation shift. In order to determine the unknowns in equation (1) we performed a non-linear least-squares analysis of the data of Table III. The results are given in Table 4 and the excellent agreement between observed and calculated shifts is shown in Figure 3. These results indicate that Ni(TMP) is about 25% dimerized at the highest concentrations used in this study. That Ni(TEP) and Ni(TPrP) do not dimerize significantly at these same concentrations indicates that aggregation is very sensitive to substitution. But aggregation must also depend on the nature of the metal system, as zinc complexes show considerable aggregation with bulkier groups (18). For Ni(TMC), if the buckled structure (19) found in the solid state persists in solution, then lack of aggregation is reasonable.

Figure 4 displays the ¹H nmr spectra of Ni(TMP) and Ni(TMC). The proton resonances in the chlorin appear at higher field than the corresponding resonances in the porphyrin. This is in complete agreement with results on their solid state structures (19). The alternating nature of the bonds in the chlorin suggests a decreased aromaticity (ring current) which is accompanied by higher field proton resonances. The difference between the two doublets of the pyrrole in Ni(TMC), 0.41 ppm, is the same as that found in H₂TPC, 0.40 ppm (20). Thus the same difference in chemical environment may be expected. The intramolecular charge transfer in the two systems may be comparable.

EXPERIMENTAL

Proton nmr spectra were determined with the use of a Varian CFT20 (80 MHz) spectrometer. Tetramethylsilane was used as an internal reference. Optical spectra were determined with a Cary 14 spectrophotometer. Elemental analysis were carried out by Galbraith Laboratories. Water and all organic solvents were degassed by bubbling nitrogen gas through them for 30 minutes.

As a general procedure 2×10^{-2} mole of the desired metal acetate is dissolved in 400 ml of glacial acetic acid containing between 2 and 5% acetic anhydride. The solution is heated in an oil bath to 80-85°. Pyrrole (5.36 g, 8×10^{-2} mole, Aldrich) and the appropriate acetal (8×10^{-2} mole, Aldrich) in 25 ml glacial acetic acid are added dropwise over a 30 minute period. The mixture is heated at 80-85° with stirring for additional 2.5 hours, after which it is filtered. The filtrate is diluted with 1 liter water and extracted with chloroform (2×250 ml). The residue is refluxed for 15 minutes in chloroform under nitrogen, the organic solvents are combined, washed with water (250 ml), and with diluted ammonia solution (2×250 ml of 10%). If the water layer is not basic, additional washing with ammonia is required. The organic solution is then washed with water (250 ml), dried on sodium sulfate, the solution is concentrated under reduced pressure to about 50 ml, and chromatographed on dry neutral alumina (Baker). The chromatography is carried out on degassed columns. The dry alumina is degassed by pumping for 10 minutes and flushing with nitrogen; this procedure is repeated 5 times. For the first chromatography, *i.e.*, for removing most of the tars, silica gel (Grace type 62) (methylene chloride) is preferred; thereafter alumina (Baker) (1:1 benzene:chloroform) is used.

(5,10,15,20-Tetramethylchlorinato) and porphinato)nickel(II).

For reaction in the presence of 2% acetic anhydride the total yield of 4:1 mixture of chlorin:porphyrin is 1.6%. For the reaction in the presence of 5% acetic anhydride the yield of the chlorin is 1.9%. Crystallization from benzene solution was carried out in a desiccator containing pentane.

Anal. Calcd. for Ni(TMP), C₂₄H₂₀N₄Ni: C, 68.12; H, 4.76; N, 13.24; Ni, 13.87. Found: C, 67.96; H, 4.79; N, 13.13; Ni, 13.69. Calcd. for Ni(TMC), C₂₄H₂₂N₄Ni: C, 67.79; H, 5.22; N, 13.18; Ni, 13.81. Found: C, 67.60; H, 5.13; N, 13.03; Ni, 14.00.

(5,10,15,20-Tetraethylporphinato)nickel(II).

For reaction in the presence of 2% acetic anhydride the yield is 3.9%.

Anal. Calcd. for C₂₈H₂₈N₄Ni: C, 70.19; H, 5.85; N, 11.70; Ni, 12.26. Found: C, 69.88; H, 5.77; N, 11.78; Ni, 11.97.

(5,10,15,20-Tetrapropylporphinato)nickel(II).

For reaction in the presence of 2% acetic anhydride the yield is 5.4%.

Anal. Calcd. for C₃₃H₃₆N₄Ni: C, 71.81; H, 6.73; N, 10.47; Ni, 10.98. Found: C, 71.61; H, 6.71; N, 10.61; Ni, 11.11.

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