The Synthesis, Properties, and Reactivities of Free-Base- and Zn(II)-*N*-Methyl Hydroporphyrin Compounds. The Unexpected Selectivity of the Direct Methylation of Free-Base Hydroporphyrin Compounds

Alan M. Stolzenberg,* Scott W. Simerly, Bryan D. Steffey, and G. Scott Haymond

Contribution from the Department of Chemistry, West Virginia University, Morgantown, West Virginia 26506

Received July 3, 1997[⊗]

Abstract: The free-base and Zn(II) complexes of *N*-methyl-*β*-octaethyl- and *meso*-tetratolylchlorin and isobacteriochlorin were synthesized and characterized. Direct methylation of free-base hydroporphyrin compounds was unexpectedly selective. Only one of the several possible regioisomers that could result from alkylation of the inequivalent N atoms was produced for each hydroporphyrin free-base. This result was independent of the electrophilic reagent ([$MeSPh_2$][BF_4] for *meso*-tetraaryl compounds and methyl trifluoromethanesulfonate for *β*-octaethyl compounds) or the peripheral substituents on the hydroporphyrin. However, the greater basicity of the *β*-octaethyl substituted compounds resulted in their isolation as protonated cations. Methylation occurred at a pyrrole ring rather than a pyrroline ring. In chlorins, the pyrrole ring across the macrocycle from the pyrroline ring was methylated to afford the symmetric *N*-methyl chlorins H(*s-N23*-MeTTC) and H_2(*s-N23*-MeOEC)$^+$. The selectivity is a result of kinetic rather than thermodynamic factors. Slow air oxidation of H(*N*-MeTTiBC) affords the unsymmetric *N*-methyl chlorin H(*u-N22*-MeTTC). The bacteriochlorins H_2(TTBC) and H_2(OEBC) were unreactive toward all electrophilic reagents investigated. An alternative synthetic approach, reduction of H(*N*-MeTTP), appears to have a selectivity complementary to direct methylation. It afforded a complex mixture of compounds that contained H(*u-N22*-MeTTC) and one other yet unidentified *N*-methyl hydroporphyrin. Free-base *N*-methyl hydroporphyrins react rapidly and quantitatively with zinc salts to afford Zn(II) complexes. The ^{1}H NMR spectra were characterized by *N*-methyl group resonances that have shifts between 0 and 4 ppm upfield of TMS and decreased ring current effects as the saturation of the macrocycle increases. The inequivalence of the two faces of the macrocycle owing to the *N*-methyl group revealed that the *meso*-aryl groups undergo restricted rotational motion. The barriers to rotation vary with saturation and metalation but are substantially smaller than in metallo-TTP compounds. Both the oxidations and reductions of free-base *N*-methyl hydroporphyrin compounds are markedly irreversible. However, the zinc complexes have reversible reductions.

Structural modification and conformational distortion of porphyrins are topics of considerable interest because of the roles that they may have in controlling the properties and functions of tetrapyrroles in biological systems.[1] Functional significance is attributed to the nonplanar conformations of the tetrapyrrole prosthetic groups in photosynthetic reaction centers,[2] photosynthetic antenna complexes,[3] the F_{430}-containing enzyme methylcoenzyme-M reductase,[4−6] heme proteins,[7] and B_{12}-dependent enzymes.[8] Nonplanar structures can result from steric constraints induced by extensive substitution of the peripheral positions, substitution of the porphyrin core, saturation of the porphyrin ring, and packing effects or protein binding interactions. The effects of combining two of these modifications have not been examined in detail. This paper reports the first results of a systematic investigation of porphyrin compounds that are both *N*-substituted and ring reduced.

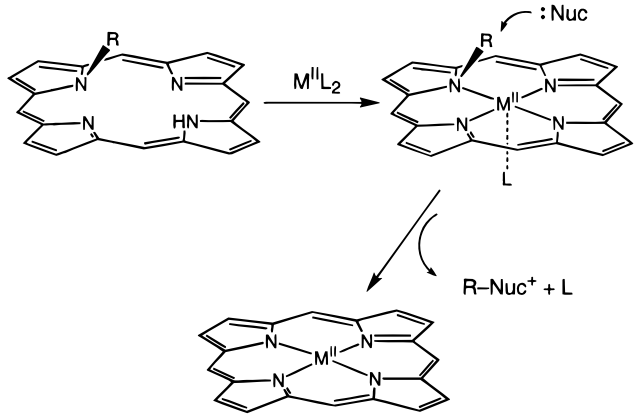
N-Substituted porphyrins evolved from laboratory curiosities into compounds of biochemical and biomedical significance during the 1980s.[9] In this decade, the "green pigments" produced by reaction of hemoproteins with certain drugs, anaesthetics, or other xenobiotics were shown to be *N*-substituted porphyrins.[10−12] These compounds are not merely byproducts of hemoprotein inactivation. Some induce porphyria-like conditions by inhibition of ferrochelatase[13−15] and heme oxygenase,[13] the enzymes of heme synthesis and degradation, respectively. Synthetic *N*-substituted porphyrins have been exploited for rapid and gentle syntheses of metalloporphyrin complexes that contain radionuclides with short half-lives.[16] The radio-labeled complexes are intended for use in medical diagnostic imaging or

[⊗] Abstract published in *Advance ACS Abstracts,* November 15, 1997.

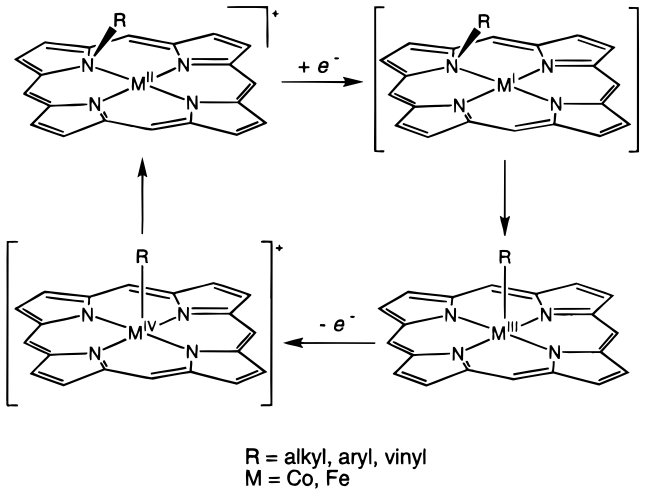
(1) Ravikanth, M.; Chandrashekar, T. K. *Struct. Bonding (Berlin)* **1995**, *82*, 105−188.
(2) Deisenhofer, J.; Michel, H. *Science* **1989**, *245*, 1463−1473.
(3) Tronrud, D. E.; Schmid, M. F.; Matthews, B. W. *J. Mol. Biol.* **1986**, *188*, 443.
(4) Eschenmoser, A. *Ann. N. Y. Acad. Sci.* **1986**, *471*, 108.
(5) Furenlid, L. R.; Renner, M. W.; Fajer, J. *J. Am. Chem. Soc.* **1990**, *112*, 8987−8989.
(6) Furenlid, L. R.; Renner, M. W.; Smith, K. M.; Fajer, J. *J. Am. Chem. Soc.* **1990**, *112*, 1634−1635.
(7) Alden, R. G.; Ondrias, M. R.; Shelnutt, J. A. *J. Am. Chem. Soc.* **1990**, *112*, 691−697.
(8) Geno, M. K.; Halpern, J. *J. Am. Chem. Soc.* **1987**, *109*, 1238−1240.
(9) Lavallee, D. K. *The Chemistry and Biochemistry of N-Substituted Porphyrins*; VCH Verlagsgesellschaft: Weinheim, Fed. Rep. Ger., 1987.
(10) Saito, S.; Itano, H. A. *Proc. Natl. Acad. Sci., U. S. A.* **1981**, *78*, 5508−5512.
(11) Ortiz de Montellano, P. R.; Kunze, K. L. *J. Am. Chem. Soc.* **1981**, *103*, 6534−6536.
(12) Augusto, O.; Kunze, K. L.; Ortiz de Montellano, P. R. *J. Biol. Chem.* **1982**, *257*, 6231−6241.
(13) De Matteis, F.; Gibbs, A. H.; Harvey, C. *Biochem. J.* **1985**, *226*, 537−544.
(14) Tephly, T. R.; Gibbs, A. H.; DeMatteis, F. *Biochem. J.* **1979**, *180*, 241−244.
(15) De Matteis, F.; Gibbs, A. H.; Holley, A. E. *Ann. N. Y. Acad. Sci.* **1987**, *514*, 30−40.

S0002-7863(97)02210-5 CCC: $14.00

Scheme 1



Scheme 2



treatment of target tissues that specifically accumulate the radiolabeled complex or an antibody conjugate of the complex.

The *in vivo* production of *N*-substituted porphyrins and the rapid and gentle metalation reactions are both direct consequences of the distinctive chemical properties of porphyrins modified by *N*-substitution. Alkylation of a nitrogen atom causes significant changes to the conformations and properties of the porphyrin macrocycle.[9] The *N*-substituent forces the macrocycle to be nonplanar and serves to expand the core. These changes significantly increase the rate of incorporation of a metal ion relative to that in a planar, more rigid porphyrin.[17,18] Under appropriate conditions, a nucleophile can remove the *N*-substituent from the pyrrolic nitrogen after incorporation of the metal ion, Scheme 1.[18−21] The expansion of the core also contributes to the ability of *N*-substituted porphyrins to stabilize lower oxidation states of metal ions than are typically observed in unmodified porphyrins. For example, Co(II), Mn(II), and Fe(II) complexes of *N*-alkyl porphyrins are air stable.[22,23] More remarkable is that Cu(I) is accessible for *N*-substituted porphyrins but not for unmodified porphyrins.[24] Other factors that contribute to the stabilization of lower oxidation states include the less negative charge of the macrocycle (monoanionic vs dianionic for unmodified porphyrin) and the weaker σ-donor strength of the tertiary, substituted pyrrolic nitrogen atom. Lower oxidation states are not accessible for all metals, though. Reduction of Fe(II), Co(II), and Ni(II) *N*-substituted porphyrin complexes results in the formal oxidative addition of the N−C bond to the metal, affording alkyl− or aryl−metal porphyrins, Scheme 2.[25−32] Reductive elimination of the pyrrolic nitrogen and carbon ligands occurs upon oxidation of alkyl- and aryl-Fe(III) and Co(III) porphyrin complexes and is responsible for the formation of the green pigments.[25,26,28,29,33] Rearrangments of *N*-substituted Ni(II) complexes can also result in insertion of the substituent between the α- and meso carbons, affording a homoporphyrin.[34]

Hydroporphyrins and their metal complexes play central roles as prosthetic groups in the biochemical pathways of the carbon, nitrogen, and sulfur cycles and in the metabolism of many anaerobes. Examples include siroheme, the iron-isobacteriochlorin prosthetic group of assimilatory (biosynthetic) nitrite and sulfite reductases;[35−37] chlorophylls, the magnesium-chlorin and bacteriochlorin pigments of photosynthesis;[38] and F_{430}, a nickel-hydrocorphinoid prosthetic group involved in methanogenesis.[39] Hydroporphyrins have intrinsically larger core sizes and exhibit both a greater tendency to adopt nonplanar conformations and greater displacements from planarity than corresponding porphyrin complexes.[40,41] Standard reduction potentials of ligand-centered redox processes generally decrease with increasing macrocycle saturation.[42−52] Thus, hydroporphyrin macrocycles are easier to oxidize and more difficult to

(16) Lavallee, D. K.; White, A.; Diaz, A.; Battioni, J. P.; Mansuy, D. *Tetrahedron Lett.* **1986**, *27*, 3521−3524.
(17) Shah, B.; Shears, B.; Hambright, P. *Inorg. Chem.* **1971**, *10*, 1828−1830.
(18) Bain-Ackerman, M. J.; Lavallee, D. K. *Inorg. Chem.* **1979**, *18*, 3358−3364.
(19) Lavallee, D. K. *Inorg. Chem.* **1976**, *15*, 691−694.
(20) Lavallee, D. K. *Inorg. Chem.* **1977**, *16*, 955−957.
(21) Stinson, C.; Hambright, P. *Inorg. Chem.* **1976**, *15*, 3181−3182.
(22) Lavallee, D. K.; Bain, M. J. *Inorg. Chem.* **1976**, *15*, 2090−2093.
(23) Anderson, O. P.; Kopelove, A. B.; Lavallee, D. K. *Inorg. Chem.* **1980**, *19*, 2101−2107.
(24) Kuila, D.; Kopelove, A. B.; Lavallee, D. K. *Inorg. Chem.* **1985**, *24*, 1443−1446.
(25) Mansuy, D.; Battioni, J. P.; Dupre, D.; Sartori, E.; Chottard, G. *J. Am. Chem. Soc.* **1982**, *104*, 6159−6161.
(26) Lancon, D.; Cocolios, P.; Guilard, R.; Kadish, K. M. *J. Am. Chem. Soc.* **1984**, *106*, 4472−4478.
(27) Ogoshi, H.; Watanabe, E.; Koketzu, N.; Yoshida, Z. *J. Chem. Soc., Chem. Commun* **1974**, *22*, 943−944.
(28) Dolphin, D.; Halko, D. J.; Johnson, E. *Inorg. Chem.* **1981**, *20*, 4348−4351.
(29) Callot, H. J.; Metz, F. *J. Chem. Soc., Chem. Commun* **1982**, *16*, 947−948.
(30) Callot, H. J.; Metz, F.; Cromer, R. *Nouv. J. Chim.* **1984**, *8*, 759−763.
(31) Callot, H. J.; Cromer, R.; Louati, A.; Gross, M. *Nouv. J. Chim.* **1984**, *8*, 765−770.
(32) Guldi, D. M.; Neta, P.; Hambright, P.; Rahimi, R. *Inorg. Chem.* **1992**, *31*, 4849−4853.
(33) Ortiz de Montellano, P. R.; Kunze, K. L.; Augusto, O. *J. Am. Chem. Soc.* **1982**, *104*, 3545−3546.
(34) Callot, H. J.; Tschamber, T. *J. Am. Chem. Soc.* **1975**, *97*, 6175−6178.
(35) Murphy, M. J.; Siegel, L. M. *J. Biol. Chem.* **1973**, *248*, 6911.
(36) Vega, J. M.; Garrett, R. H.; Siegel, L. M. *J. Biol. Chem.* **1975**, *250*, 7980.
(37) Vega, J. M.; Kamin, H. *J. Biol. Chem.* **1977**, *252*, 896.
(38) *Chlorophylls*; Scheer, H., Ed.; CRC Press: Boca Raton, FL, 1991.
(39) Ellefson, W. L.; Whitman, W. B.; Wolfe, R. S. *Proc. Natl. Acad. Sci. U.S.A.* **1982**, *79*, 3707−3710.
(40) Scheidt, W. R.; Lee, Y. J. *Struct. Bonding (Berlin)* **1987**, *64*, 1−70.
(41) Stolzenberg, A. M.; Schussel, L. J.; Summers, J. S.; Foxman, B. M.; Petersen, J. L. *Inorg. Chem.* **1992**, *31*, 1678−1686.
(42) Stolzenberg, A. M.; Spreer, L. O.; Holm, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 364−370.
(43) Stolzenberg, A. M.; Strauss, S. H.; Holm, R. H. *J. Am. Chem. Soc.* **1981**, *103*, 4763−4778.
(44) Stolzenberg, A. M.; Stershic, M. T. *Inorg. Chem.* **1987**, *26*, 1970.
(45) Stolzenberg, A. M.; Stershic, M. T. *Inorg. Chem.* **1988**, *27*, 1614.
(46) Stolzenberg, A. M.; Stershic, M. T. *Inorg. Chem.* **1987**, *26*, 3082−3083.
(47) Stolzenberg, A. M.; Stershic, M. T. *J. Am. Chem. Soc.* **1988**, *110*, 6391−6402.
(48) Stolzenberg, A. M.; Schussel, L. J. *Inorg. Chem.* **1991**, *30*, 3205−3213.
(49) Richardson, P. F.; Chang, C. K.; Spaulding, L. D.; Fajer, J. *J. Am. Chem. Soc.* **1979**, *101*, 7736−7738.

reduce than porphyrins. The resistance of the macrocycle to reduction and the larger core size are reasons that hydroporphyrin ligands, like *N*-substituted porphyrins, can stabilize metal ions in less common, low-valent oxidation states like Cu(I) and Ni(I), which are inaccessible in porphyrins.[46−48] Stability constants for ligand binding to metal complexes generally increase with increasing saturation of the macrocycle.[53]

In this paper, we describe the syntheses and properties of the free-base and Zn(II) complexes of *N*-substituted hydroporphyrin compounds. Only one example of this class of compounds has been reported previously.[54,55] Our study included both *meso*-tetraaryl- and β-octaalkyl-substituted precursor compounds. Thus, the effects of the peripheral substitution on reactions producing *N*-substituted hydroporphyrin compounds and on the properties of these compounds were apparent. The reactions affording *N*-substituted hydroporphyrin compounds are surprisingly selective. Only one of the several possible isomeric *N*-substituted hydroporphyrin compounds was obtained in each case.

Results and Discussion

Synthesis. Synthesis of *N*-substituted hydroporphyrin compounds requires two modifications of the parent porphyrin compound, reduction of one or more double bonds in the porphyrin π-system, and introduction of a substituent on a nitrogen atom. The reactions that have been used to achieve these modifications, below, have features that made it uncertain whether substitution followed by reduction or reduction followed by substitution would both be successful synthetic strategies for the production of *N*-substituted hydroporphyrins. Thus, we investigated both approaches. In either case, the first modification will lower the symmetry of the compound. Consequently, two or more isomeric *N*-substituted products are possible for each hydroporphyrin.

N-Substituted porphyrins can be synthesized by reaction of a free-base porphyrin and an electrophilic reagent when the substituent is an alkyl, benzyl, or allyl group. The reagents employed include alkyl iodides;[56] dialkyl sulfates;[57] alkylfluorosulfonates;[54,58] alkyltrifluoromethanesulfonates;[9] and alkyl-, benzyl-, and allyldiphenylsulfonium salts.[16,59] Reaction conditions vary from ambient temperature and pressure to sealed tube reactions and temperatures in excess of 140 °C. Yields of mono-*N*-substituted porphyrins are frequently low, especially for substituents with steric bulk greater than methyl. Use of excess electrophilic reagent increases the formation of *N*,*N*′-di- and *N*,*N*′,*N*″-trisubstituted compounds. Aryl and vinyl substituents cannot be introduced directly. The best preparative methods for these substituents involve the oxidatively induced migration of a σ-aryl, σ-vinyl, or σ-carbene complex of Fe(III) or Co(III) porphyrin.[9,30,31] We restricted our investigation to *N*-methyl substituted hydroporphyrin compounds in order to limit the synthetic complexity and to take advantage of the greater available range of methylating agents.

The reagent of choice to reduce porphyrins to hydroporphyrins depends upon the substitution of the porphyrin. For H_2(TPP)[60] the standard method is reduction by diimide, N_2H_2, generated *in situ* from *p*-toluenesulfonhydrazide.[61] The initial product is the dihydroporphyrin H_2(TPC). Continued reduction of free-base compounds with a larger quantity of diimide affords the tetrahydroporphyrin H_2(TPBC). In contrast, extended reduction of Zn(TPP) or Zn(TPC) affords the isomeric tetrahydroporphyrin H_2(TPiBC) after workup. Although gram-scale quantities of material can be prepared by this method, the materials obtained are mixtures of the various compounds that contain at best 80−90% of the target hydroporphyrin. The quinone reoxidations and phosphoric acid extractions that were reported to afford pure materials[61] did not work in our hands. Tetraphenylhydroporphyrins are not readily separable by chromatography because reduction changes neither the shape nor polarity of the molecules to a significant extent. Pure compounds can be obtained by chromatography but only on a tens of milligram scale. Diimide is not a practical reagent for reduction of β-octaalkyl-substituted porphyrins because it hydrogenates with *cis* selectivity. The severe steric interactions between the resulting eclipsed *cis*-alkyl substituents leads to a low yield of the chlorin and to the extreme sensitivity of the chlorin to reoxidation.[44] Octaalkylporphyrins are typically reduced with sodium metal in isoamyl alcohol.[42,62−64] The strongly basic conditions of the reaction results in equilibration to the thermodynamically preferred *trans*-hydrogenation product but requires use of the iron complex rather than the free-base to prevent formation of the nonreducible porphyrin dianion. With proper manipulation of the reaction conditions, gram quantities of chlorin can be obtained pure without chromatography. Continued reduction of the metal complex favors the isobacteriochlorin. Only traces of the bacteriochlorin are produced. The crude isobacteriochlorin is readily purified on a 50−100 mg scale by chromatography on MgO.

Our initial efforts to prepare *N*-substituted hydroporphyrins examined the reduction of *N*-methyl porphyrin compounds. We did not attempt the reduction of *N*-MeOEP because the *N*-methyl group of Fe(*N*-MeOEP)Cl was expected to be lost during the sodium metal in isoamyl alcohol reduction either through reduction induced migration to iron or through nucleophilic cleavage by alkoxide anion. The reduction of H(*N*-MeTTP) by *p*-toluenesulfonhydrazide in pyridine at 100 °C produced a mixture of compounds. The ^{1}H NMR spectrum exhibited singlets at −2.10 and −3.10 ppm. Upfield shifts are characteristic of the *N*-methyl group in both *N*-methyl porphyrins[9] and hydroporphyrins, below. However, the multitude of resonances in the *meso*-tolyl *p*-CH_3 region of the spectrum suggested that numerous other compounds were present. Subsequently, we established that the singlet at −3.10 ppm and other features

(50) Chang, C. K.; Fajer, J. *J. Am. Chem. Soc.* **1980**, *102*, 848−851.
(51) Chang, C. K.; Hanson, L. K.; Richardson, P. F.; Young, R.; Fajer, J. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 2652−2656.
(52) Choi, I.-K.; Ryan, M. D. *New J. Chem.* **1992**, *16*, 591.
(53) Summers, J. S.; Stolzenberg, A. M. *J. Am. Chem. Soc.* **1993**, *115*, 10559−10567.
(54) Grigg, R.; Sweeney, A.; Dearden, G. R.; Jackson, A. H.; Johnson, A. W. *J. Chem. Soc., Chem. Commun.* **1970**, 1273−1274.
(55) Grigg, R.; Shelton, G.; Sweeney, A.; Johnson, A. W. *J. Chem. Soc., Perkin Trans. I* **1972**, 1789−1799.
(56) McEwen, W. K. *J. Am. Chem. Soc.* **1946**, *68*, 711−713.
(57) Latos-Grazynski, L. *Inorg. Chem.* **1985**, *24*, 1681−1686.
(58) Lavallee, D. K.; Gebala, A. E. *Inorg. Chem.* **1974**, *13*, 2004−2008.
(59) Balch, A. L.; Cornman, C. R.; Latos-Grazynski, L.; Olmstead, M. M. *J. Am. Chem. Soc.* **1990**, *112*, 7552−7558.

(60) Abbreviations: OEP, 2,3,7,8,12,13,17,18-octaethylporphyrin dianion; OEC, 2,3-dihydro-2,3,7,8,12,13,17,18-octaethylporphyrin dianion (chlorin); OEBC, 2,3,12,13-tetrahydro-2,3,7,8,12,13,17,18-octaethylporphyrin dianion (bacteriochlorin); OEiBC, mixture of ttt- and tct-2,3,7,8-tetrahydro-2,3,7,8,12,13,17,18-octaethylporphyrin dianion (isobacteriochlorin); TPP, 5,10,15,20-tetraphenylporphyrin dianion; TTP, 5,10,15,20-tetra(4-methylphenyl)porphyrin dianion (i.e., tetratolylporphyrin dianion); TXP, 5,10,15,20-tetra(3,5-dimethylphenyl)porphyrin dianion (i.e. tetraxylylporphyrin dianion); T*p*FPP, 5,10,15,20-tetra(4-fluorophenyl)porphyrin dianion; T*p*NO_2PP, 5,10,15,20-tetra(4-nitrophenyl)porphyrin dianion; TTC, 2,3-dihydro-5,10,15,20-tetratolylporphyrin dianion (tetratolylchlorin); TTBC, 2,3,12,13-tetrahydro-5,10,15,20-tetratolylporphyrin dianion (tetratolylbacteriochlorin); TTiBC, 2,3,7,8-tetrahydro-5,10,15,20-tetratolylporphyrin dianion (tetratolylisobacteriochlorin).

(61) Whitlock, H. W., Jr.; Hanauer, R.; Oester, M. Y.; Bower, B. K. *J. Am. Chem. Soc.* **1969**, *91*, 7485−7489.
(62) Fischer, H.; Helberger, H. *Liebigs Ann. Chem.* **1929**, *471*, 285.
(63) Eisner, U.; Lichtarowicz, A.; Linstead, R. P. *J. Chem. Soc.* **1957**, 733−738.
(64) Eisner, U. *J. Chem. Soc.* **1957**, 3461−3469.

observed in the spectrum were due to the presence of H(*u-N22*-MeTTC). We have not identified the compound responsible for the singlet at −2.10 ppm, but its shift might be consistent with the isomeric H(*s-N21*-MeTTC) or with an *N*-MeTTBC compound. We did not pursue this synthetic strategy further because preliminary attempts to separate the product mixture appeared less than promising and suggested yields would be low. Recently, Krattinger and Callot reported that *p*-toluenesulfonhydrazide or borohydride reduction of *N*-MeTTP and *N*-PhTTP afford *N*-substituted phlorin rather than *N*-substituted hydroporphyrin compounds.[65,66] We see no evidence for *N*-methyl-*meso*-tetratolylphlorin in the ^{1}H NMR spectrum of the mixture that we obtained. We are uncertain whether the different results are a consequence of the difference in substitution of the porphyrins investigated, the lower reaction temperature that we used, or a difference in workup procedures.

We next proceeded to investigate the *N*-alkylation of hydroporphyrin compounds. Our choice to use tetraphenylporphyrin compounds with *para*-substituted *meso*-phenyl groups in this work required us to first investigate and optimize the previously unreported reductions of the substituted porphyrin compounds. These compounds were chosen to simplify the interpretation of the ^{1}H NMR spectra of the products. Both the reduction of a porphyrin to a hydroporphyrin and the introduction of an *N*-substituent break the 4-fold symmetry of the porphyrin. This, in turn, increases the number of peaks observed in the spectrum. Replacement of the phenyl *para*-H atom with a group that does not spin couple with the *ortho*- and *para*-H atoms simplifies the latters' resonances from multiplets to two doublets with a characteristic coupling constant of roughly 7.6 Hz. The doublets are more readily resolved and assigned than the multiplets and can be easily distinguished from pyrrole β-H doublets, which have a characteristic coupling constant of about 4.5 Hz. In addition, use of a methyl or methoxy group as the *para*-substituent affords sharp singlets that can effectively report the symmetries of the compounds.

The electronic nature of the phenyl substituent has a substantial effect on the rate of the diimide reduction of substituted tetraphenylporphyrin compounds relative to the unsubstituted H_2(TPP). Electron donating groups like methyl slow the rate and require extended reaction times and addition of greater excesses of *p*-toluenesulfonhydrazide. The reduction step from porphyrin to chlorin is slowed to a greater extent than subsequent reduction steps. Thus, if the reduction is run until all porphyrin is consumed, significantly greater quantities of the bacteriochlorin H_2(TTBC) is produced from H_2(TTP) than H_2(TPBC) is produced from H_2(TPP). Moreover, significant quantities of overreduced, hexahydroporphyrin products are formed during the subsequent phase of the reaction in which the remaining H_2(TTC) is reduced to H_2(TTBC). The reduction of H_2(TXP) was even more difficult than that of H_2(TTP). Electron withdrawing substituents such as nitro and fluoro groups increase the rate of reduction. However, we did not pursue these compounds in this investigation because of their less informative NMR spectra, the limited solubility of H_2(T*p*FPP), and the difficulty of removing the large amounts of nonporphyrin byproducts formed in the synthesis of H_2(T*p*NO_2-PP).

Small samples of highly purified tetraarylhydroporphyrins were used in the preparation of *N*-methyl hydroporphyrins. We examined the extent to which reoxidation of tetrahydroporphyrin to dihydroporphyrin or dihydroporphyrin to porphyrin accompanies the alkylation reaction. With an appropriate choice of electrophile and workup conditions, below, reoxidation is not a significant problem but does occur to a small extent. We found that the chromatographic separation of the various *N*-methyl-porphyrin and -hydroporphyrin products from each other and from unreacted starting materials can be conducted on a larger scale and is substantially easier than the separation of the various hydroporphyrins. Thus, it is more efficient to use 80−90% pure mixtures than highly purified tetraarylhydroporphyrins as starting material in the alkylation reactions because larger quantities of *N*-substituted hydroporphyrins can be obtained and a chromatographic separation would still be required after alkylation to remove any small amounts of oxidized compound that might form. Subsequent work was performed with these mixtures.

The electrophiles investigated in this studied showed considerably different reactivities toward *meso*-tetraaryl- and β-octaalkyl-substituted porphyrins. The best reagent for use with the *meso*-tetraaryl-substituted porphyrins is methyldiphenylsulfonium tetrafluoroborate in *o*-dichlorobenzene solution at 130°C. Conversion to the *N*-substituted compound is less than complete, even with a 2-fold excess of the sulfonium salt, but little if any *N,N*′-dimethyl compound forms. The sulfonium salt does not have adequate reactivity toward β-octaethyl compounds or toward *meso*-tetraxylyl compounds. Only small amounts of H_2(*N*-MeOEP)$^+$ are obtained from H_2(OEP) with this reagent in *o*-dichlorobenzene solution at 130°C. The hydroporphyrins H_2(OEC) and H_2(OEiBC) are oxidized to H_2(*N*-MeOEP)$^+$ upon methylation under these presumably anaerobic conditions. It is not clear whether this reflects the instability of the hydroporphyrin or the *N*-methylhydroporphyrin to the elevated reaction temperature or to the presence of an unidentified oxidant. No reaction occurs between octaethyl compounds and the sulfonium salt in refluxing methylene chloride. Dimethyl sulfate also requires elevated temperature for a reaction to proceed. Both H_2(TTP) and H_2(OEP) are partially converted to their respective *N*-methyl compounds by this reagent in refluxing *o*-dichlorobenzene solution. However, hydroporphyrins in both series are reoxidized to porphyrin. Reactions of methyl iodide, methyl fluorosulfonate, and methyl trifluoromethylsulfonate with the octaethyl compounds proceed at room temperature in methylene chloride solution without significant oxidation of the hydroporphyrins or formation of *N,N*′-dimethyl compounds. The three electrophiles do not give satisfactory results with *meso*-tetraaryl porphyrin compounds. The *meso*-tetratolylhydroporphyrins afford mostly H(*N*-MeTTP) and H_2(TTP) affords significant amounts of (*N,N*′-Me_2TTP), even at room temperature.

The greater propensity of H_2(TTP) to form an *N,N*′-dimethyl compound with methyl iodide or methyl sulfonate esters is a consequence of the trends in basicity of the porphyrin compounds. *N*-Substituted porphyrins are stronger bases than the corresponding non-*N*-substituted porphyrin.[67,68] Whether *N*-substituted or not, β-octaalkyl-substituted porphyrins are stronger bases than meso-tetraarylsubstituted porphyrins.[9,58] The *N*-MeOEP anion is a sufficiently strong base that it retains both protons of the free-base precursor to a significant extent. H_2(*N*-MeOEP)$^+$ does not react further with the electrophile. The less basic *N*-MeTTP anion is more readily available in its neutral monoprotonated form H(*N*-MeTTP), which is a stronger nucleophile and hence more reactive than the starting neutral H_2(TTP).

The trends in basicity observed for porphyrins also hold true

(65) Krattinger, B.; Callot, H. J. *Tetrahedron Lett.* **1996**, *37*, 7699−7702.
(66) Krattinger, B.; Callot, H. J. *Chem. Commun.* **1996**, 1341−1342.
(67) Neuberger, A.; Scott, J. J. *Proc. Roy. Soc. A* **1952**, *213*, 307−326.
(68) Grigg, R.; Hamilton, R. J.; Jozefowicz, M. L.; Rochester, C. H.; Terrell, R. J.; Wickwar, H. *J. Chem. Soc., Perkin Trans. II* **1973**, 407−413.

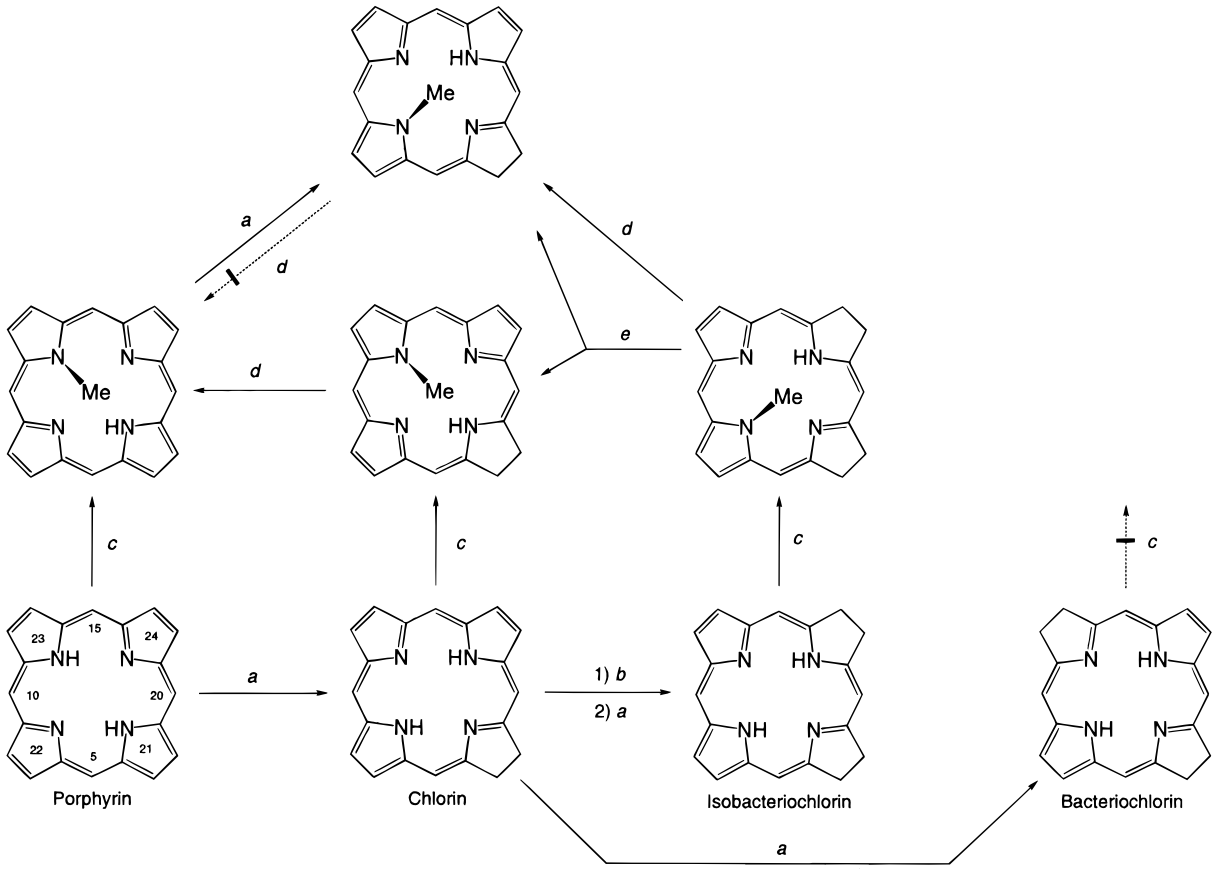


Figure 1. Structural diagrams and reaction scheme for free-base *meso*-tetratolyltetrapyrrole compounds. The tolyl groups are omitted for sake of clarity. Other resonance and tautomeric structures may exist for each compound. Porphyrin nitrogen and *meso*-carbon atoms are labeled according to IUPAC convention. Saturated β-carbon atoms in hydroporphyrins receive lowest position numbers (i.e., 2,3, etc.). Conditions *a*: excess *p*-toluenesulfonhydrazide and K_2CO_3 in pyridine at 100 °C. *b*: $Zn(OAc)_2 \cdot 2H_2O$ in pyridine. *c*: $[MeSPh_2][BF_4]$ in *o*-dichlorobenzene at 130 °C. *d*: O_2. *e*: DDQ or $[(p\text{-}BrC_6H_4)_3N][SbCl_6]$.

for the hydroporphyrin compounds. Water or acidic impurities in the solvent readily protonate *N*-alkyl-*meso*-tetraarylporphyrins and -hydroporphyrins, particularly in dilute solution. However, the neutral species can be readily obtained in purified solvents. Treatment of NMR solvents by passing them through a small column of dry, basic activated alumina (grade 1) prior to use is sufficient to prevent line broadening in the ^{1}H NMR spectrum that results from proton exchange between the neutral compound and its protonated cation. (However, broadening of the N-H resonance is not eliminated.) On the other hand, the β-octaalkyl-*N*-alkyl-substituted hydroporphyrins are sufficiently basic that with the exception of H_2(*N*-MeOEiBC)$^+$ their cations can not be fully deprotonated to the neutral compounds with pyridine or alkyl amine bases. Given these differences in basicity, we used basic alumina for the chromatographic purification of the neutral *N*-alkyl-*meso*-tetraaryl-substituted compounds and neutral alumina for the cationic *N*-alkyl-β-octaalkyl-substituted compounds.

Methylation of the *meso*-tetraarylhydroporphyrin compounds is unexpectedly selective. Alkylation or arylation of unsymmetrical porphyrins results in mixtures of regioisomers that differ with respect to which N atom is alkylated.[11,69,70] In contrast, the reaction of H_2(TTC) with methyldiphenylsulfonium tetrafluoroborate and other electrophiles affords only one of the three possible H(*N*-MeTTC) products. The ^{1}H NMR spectrum, below, establishes that the product has 2-fold symmetry. This requires that methylation occurs at either N(21) or N(23), Figure 1. For reasons discussed below, we assigned the structure of this symmetrical chlorin compound, H(*s*-*N23*-MeTTC), to be the isomer in which methylation occurred on the nitrogen atom of the unsaturated pyrrole ring, N(23), rather than on the saturated pyrroline ring, N(21). Similarly, methylation of H_2-(TTiBC) affords only one of the two possible H(*N*-MeTTiBC) products. We assigned the structure of this compound to be the isomer in which methylation occurred on the nitrogen atom of the unsaturated pyrrole ring, N(23), in Figure 1.

All attempts failed to directly methylate H_2(TTBC). This result reflects the inertness of H_2(TTBC) rather than the lability of H(*N*-MeTTBC) under the reaction conditions. The small quantity of H_2(TTBC) present as an impurity in other tetratolylhydroporphyrins survived intact the reactions that methylated these other compounds.

The selective formation of H(*s*-*N23*-MeTTC) is a consequence of kinetic rather than thermodynamic factors. A solution of H(*N*-MeTTiBC) oxidized when a slow recrystallization was attempted. The crystalline product obtained was identified by ^{1}H NMR to be the previously unobserved unsymmetrical product H(*u*-*N*-MeTTC), which has the methyl group at N(22). No other *N*-methyl porphyrin or hydroporphyrin compound was detected in the supernatant liquor over the crystals. Deliberate exposure of solutions of H(*N*-MeTTiBC) to air affords the same result. However, rapid oxidation of H(*N*-MeTTiBC) by the quinone DDQ or by tris(*p*-bromophenyl)amminium hexachloroantimonate affords a mixture of H(*s*-*N23*-MeTTC) and H(*u*-*N22*-MeTTC). Thus, assuming the *N*-methyl group does not migrate from one nitrogen to another upon oxidation, the mixture

(69) Cavaleiro, J. A. S.; Condesso, M. F. P. N.; Jackson, A. H.; Neves, M. G. P. M. S.; Rao, K. R. N.; Sadashiva, B. K. *Tetrahedron Lett.* **1984**, *25*, 6047−6048.

(70) Pandey, R. K.; Jackson, A. H.; Smith, K. M. *J. Chem. Soc., Perkin Trans I* **1991**, 1211−1220.

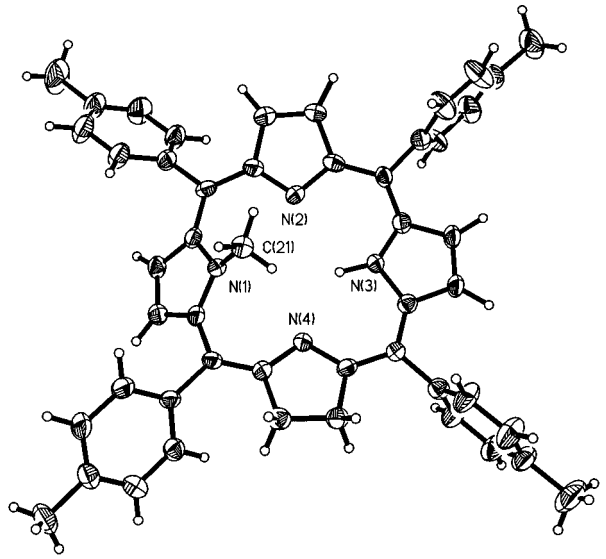


Figure 2. ORTEP diagram of the molecular structure of H(*u-N22*-MeTTC), $C_{49}H_{42}N_4$. Thermal ellipsoids are scaled to enclose 30% probablility. The N atoms are not labeled according to IUPAC convention, in which N(1) = N22 and N(4) = N21.

obtained upon oxidation fixes the *N*-methyl group of H(*N*-MeTTiBC) at N(23). (The numbering of the individual N atom changes because of the change in the relative location of the pyrroline ring β-H atom that determines the numbering scheme.) Moreover, the slow, presumably O_2-induced oxidation of H(*N*-MeTTiBC) occurs solely at the saturated pyrroline ring across the macrocycle from the pyrrole ring substituted with the *N*-methyl group. H(*u-N22*-MeTTC) can be recrystallized without oxidation. In contrast, H(*s-N23*-MeTTC) is oxidized to H(*N*-MeTTP) during attempts to grow crystals of high quality. The transformations of these compounds are summarized in Figure 1.

The structure of H(*u-N22*-MeTTC) was confirmed by X-ray crystallography, Figure 2.[71] Although the atomic positions for the non-hydrogen atoms of the *N*-methyl chlorin were well behaved with no indication of the presence of a structural disorder or excessive thermal motion, the overall quality of the structure refinement was limited by the presence of disordered solvent molecule(s) which could not be identified and modelled. The solid is a porphyrin sponge clathrate that includes channels of extensively disordered solvent.[72−74] The elemental analyses of the crystals were consistent with the presence of less than 1 equiv of hexane. The bonds and angles of H(*u-N22*-MeTTC) are indistinguishable from corresponding features in *N*-substituted porphyrins and in tetraarylhydroporphyrins.[9,75] Given the significant errors of the structure determination, these data are not reported herein. The rotation of the *N*-methyl substituted pyrrole ring out of the plane of the other three N atoms is also typical of *N*-substituted porphyrins.[9] The rotation toward the porphyrin plane of the tolyl groups adjacent to the *N*-methyl substituted pyrrole ring is noteworthy. Attempts to grow crystals of H(*u-N22*-MeTTC) that had both ordered solvent guests and fully occupied solvent sites by recrystallization in other solvent systems or by addition of specific xylene isomers were unsuccessful.

Direct alkylation of octaethylhydroporphyrins shows the same selectivity as seen with the *meso*-tetraarylhydroporphryins. The chlorin *t*-H_2(OEC) affords a single regioisomer of *t*-H_2(*N*-MeOEC)$^+$ that has mirror symmetry. Difference NOE experiments, below, confirm that the isomer obtained has the methyl group on the nitrogen atom of the unsaturated pyrrole ring, N(23), in Figure 1. Methylation of H_2(OEiBC), which is an unequal mixture of the racemic *ttt*- and meso *tct*- diastereomers, affords a mixture of diastereomers. The relative intensities of the ^{1}H NMR resonances of the *N*-methyl and *meso*-CH groups and the narrow chemical shift range of the *N*-methyl resonances are consistent with a mixture that contains the four diastereomers that result from regiospecific methylation at N(23) (or the symmetry equivalent N(24)) of the two enantiomers of the *tct*-diastereomer and of the two inequivalent faces of the *tct*-diastereomer. When partially purified samples of H_2(OEC) or H_2(OEiBC) that contain traces of H_2(OEBC) are reacted with the electrophiles studied herein, none of the H_2(OEBC) is methylated. Thus, regardless of their peripheral substitution, bacteriochlorins are particularly resistant to direct *N*-alkylation.

Attempts to prepare unsymmetrical H_2(*N*-MeOEC)$^+$ were not successful. H_2(*N*-MeOEiBC)$^+$ is not readily oxidized by air, owing to its protonation and cationic charge. Oxidants that are sufficiently strong to oxidize the cation do not stop at the chlorin level of reduction. H_2(*N*-MeOEiBC)$^+$ is sensitive to decomposition to unidentified products during storage and during column chromatography if the residence time on the column is longer than typical for a flash column separation.

The free-base *N*-methyl-*meso*-tetraaryl- and -β-octaalkylhydroporphyrins react readily and quantitatively with various salts of Zn(II), Cu(II), Co(II) and other transition metals in several different solvent systems to afford metal complexes. Complex formation is evident from changes in the UV−vis and ^{1}H NMR spectra of the compounds. We confine our attention in this paper to the diamagnetic Zn(II) complexes. A neutral complex of a divalent metal ion like Zn(II) must retain an anion as either a counterion or ligand because the deprotonated *N*-substituted compounds are monoanionic ligands. We have not yet achieved complete characterization of the Zn(II) complexes because we were unable to obtain recrystallized samples suitable for analysis. In addition, spectroscopic data did not establish unequivocally whether the anion is an acetate or chloride from the metal salt or a solvent derived anion such as hydroxide. Metathesis experiments in which the Zn(II) complex of an *N*-methyl-tetratolylhydroporphyrin was equilibrated with aqueous solutions of sodium chloride, bromide, iodide, acetate, or hydroxide showed little effect of the anion on the UV−vis, fluorescence, or ^{1}H NMR spectra. One exception was [Zn(*N*-MeTTiBC)]$^+$, for which the intensity ratio of the two fluorescence emission bands and *N*-methyl resonance shift varied reproducibly with anion. Moreover, two separate *N*-methyl resonances were observed in some cases when equilibration was incomplete. The total range of variation of the shift was only about 0.2 ppm. Given the small size of the effect, it is not certain that the anion is a ligand rather than a counterion. Extrapolation of structural studies of M^{II}(*N*-MeTPP)Cl complexes suggests the former.[9] The spectrum of Zn(*s-N23*-MeOEC)$^+$ also suggests the anion serves as a ligand. We observed two sets of *meso*-CH and *N*-methyl resonances that

(71) Crystallographic data for $C_{49}H_{42}N_4$ hexane solvate: triclinic, $P\bar{1}$, a = 10.490(1) Å, b = 14.610(1) Å, c = 14.690(1), α = 96.640(7)°, β = 97.930(6)°, γ = 93.069(7)°, V = 2197.2(3) Å^3, Z = 2, ρ_c = 1.147 g/cm^3, T = 295(2) K. Full-matrix anisotropic refinement (on F_o^2) of 532 parameters was halted at R = 0.0990 and wR = 0.1028 for 3319 data with $F > 2s(F)$ and GOF = 1.81. The disordered hexane solvent could not be satisfactorily modeled.

(72) Byrn, M. P.; Curtis, C. J.; Khan, S. I.; Sawin, P. A.; Tsurumi, R.; Strouse, C. E. *J. Am. Chem. Soc.* **1990**, *112*, 1865−1874.

(73) Byrn, M. P.; Strouse, C. E. *J. Am. Chem. Soc.* **1991**, *113*, 2501−2508.

(74) Byrn, M. P.; Curtis, C. J.; Goldberg, I.; Hsiou, Y.; Khan, S. I.; Sawin, P. A.; Tendick, S. K.; Strouse, C. E. *J. Am. Chem. Soc.* **1991**, *113*, 6549−6557.

(75) Barkigia, K.; Miura, M.; Thompson, M. A.; Fajer, J. *Inorg. Chem.* **1991**, *30*, 2233−2236.

Table 1. ^{1}H NMR Data for Free-Base and Zn(II) *N*-Methyl-*meso*-tolylporphyrin and -hydroporphyrin Compounds[a]

compd	N-H or N-CH_3	*p*-tolyl-CH_3	CH_2-CH_2	*m*-tolyl	*o*-tolyl	pyrrole-H
H_2(TTP)	−2.78 (s, 2H)	2.71 (s, 12H)		7.55 (d, 7.9 Hz, 8H)	8.10 (d, 7.9 Hz, 8H)	8.86 (s, 8H)
H_2(TTC)	−1.45 (s, 2H)	2.62 (s, 6H), 2.65 (s, 6H)	4.15 (s, 4H)	7.48 (d, 7.9 Hz, 8H)	7.74 (d, 7.9 Hz, 4H), 7.98 (d, 7.9 Hz, 4H)	8.17 (d, 4.9 Hz, 2H), 8.42 (s, 2H), 8.57 (d, 4.9 Hz, 2H)
H_2(TTBC)	−1.36 (s, 2H)	2.59 (s, 12H)	3.97 (s, 8H)	7.43 (d, 7.9 Hz, 8H)	7.68 (d, 7.9 Hz, 8H)	7.92 (4H)
H_2(TTiBC)	0.82 (s, 2H)	2.41 (s, 3H), 2.44 (s, 6H), 2.47 (s, 3H)	3.20 (m, br, 8H)	7.31 (br, 6H),[b] 7.43 (d, 7.9 Hz, 2H)[b]	7.29 (d, 7.9 Hz, 2H),[b] 7.44 (d, 7.9 Hz, 4H),[b] 7.64 (d, 7.9 Hz, 2H)	6.88 (d, 4.6 Hz, 2H), 7.39 (d, 4.3 Hz, 2H)
H(*N*-MeTTP)	−4.09 (s, 3H)	2.70 (s, 6H), 2.69 (s, 6H)		7.56 (d, 7.9 Hz, 4H), 7.64 (d, 7.9 Hz, 4H)	8.14 (m, br, 4H), 8.27 (m, br, 4H)	7.40 (s, 2H), 8.46 (d, 4.6 Hz, 2H), 8.64 (d, 4.6 Hz, 2H), 8.83 (s, 2H)
H(*u-N22*-MeTTC)	−3.10 (s, 3H), −0.60 (br, 1H)	2.61 (s, 6H), 2.64 (s, 6H)	3.7−4 (2H), 4.2 (1H), 4.5 (1H), cmplx m	7.48 (d, 7.9 Hz, 4H), 7.53 (d, 8.5 Hz, 2H), 7.70 (d, 7.6 Hz, 2H)	7.74 (d, 7.3 Hz, 2H), 7.85 (d, 7.9 Hz, 4H), 7.96 (m, br, 2H)	7.08 (d, 4.6 Hz, 1H), 7.24 (d, 4.6 Hz, 1H), 8.04 (d, 5.2 Hz, 1H), 8.10 (d, 4.3 Hz, 1H), 8.31 (d, 4.6 Hz, 1H), 8.44 (d, 4.9 Hz, 1H)
H(*s-N23*-MeTTC)	−2.45 (s, 3H)	2.61 (s, 6H), 2.65 (s, 6H)	3.65 (d, 12 Hz, 2H), 4.16 (d, 12 Hz, 2H)	7.45 (d, 7.9 Hz, 4H), 7.56 (d, 7.9 Hz, 4H)	7.6−7.9 (br, 4H), 8.08 (d, 7.6 Hz, 4H)	7.13 (s, 2H), 7.81 (d, 4.6 Hz, 2H), 8.26 (d, 4.6 Hz, 2H)
H(*N*-MeTTiBC)	−1.02 (s, 3H)	2.50 (s, 3H), 2.52 (s, 3H), 2.53 (s, 3H), 2.56 (s, 3H)	3.2−3.7, 3.8−4.0, (m, 8H)	7.3−7.5 (br, 4H),[b] 7.36 (d, 6.7 Hz, 2H),[b] 7.57 (d, 7.0 Hz, 2H)	7.3−7.5 (br, 2H),[b] 7.40 (d, 8.2 Hz, 2H), 7.65 (d, 8.0 Hz, 2H), 7.86 (d, 7.7 Hz, 2H)	6.66 (d, 4.4 Hz, 1H), 6.75 (d, 4.4 Hz, 1H), 7.31 (d, 4.7 Hz, 1H), 7.92 (d, 4.9 Hz, 1H)
Zn(*N*-MeTTP)$^{+}$[c]	−3.87 (s, 3H)	2.71 (s, 6H), 2.72 (s, 6H)		7.53 (d, 7.6 Hz, 2H), 7.56 (d, 7.6 Hz, 2H), 7.63 (d, 7.6 Hz, 2H), 7.70 (d, 7.6 Hz, 2H)	8.00 (d, 7.6 Hz, 2H), 8.15 (d, 7.6 Hz, 2H), 8.18 (d, 7.6 Hz, 2H), 8.45 (d, 7.6 Hz, 2H)	8.24 (s, 2H), 8.82 (d, 4.8 Hz, 2H), 8.89 (s, 2H), 8.93 (d, 4.8 Hz, 2H)
Zn(*u-N22*-MeTTC)$^{+}$	−2.60 (s, 3H)	2.63 (s, 3H), 2.64 (s, 3H), 2.67 (s, 3H), 2.68 (s, 3H)	3.90, 4.05, 4.30, 4.58, (m, 1H ea)	*d*	*d*	7.71 (d, 4.5 Hz, 1H), 8.09 (d, 4.9 Hz, 1H), 8.12 (d, 4.3 Hz, 1H), 8.36 (d, 4.6 Hz, 1H), 8.48 (d, 4.8 Hz, 1H), 8.50 (d, 4.6 Hz, 1H)
Zn(*s-N23*-MeTTC)$^{+}$	−1.84 (s, 3H)	2.59 (s, 6H), 2.64 (s, 6H)	3.91 (sm), 3.95 (lg), 4.00 (lg), 4.04 (sm), AB quartet	7.43 (d, 7.8 Hz, 4H), 7.54 (d, 7.8 Hz, 4H)	7.64 (d, 7.8 Hz, 2H), 7.69 (d, 7.8 Hz, 2H), 8.01 (br, 4H)	7.48 (s, 2H), 7.97 (d, 4.8 Hz, 2H), 8.46 (d, 4.8 Hz, 2H)
Zn(*N*-MeTTiBC)$^{+}$	0.29 (s, 3H)	2.43 (s, 3H), 2.47 (s, 3H), 2.48 (s, 3H), 2.52 (s, 3H)	2.9−3.8, (m, 8H)	*d*	*d*	6.64 (d, 3.7 Hz, 1H), 6.94 (d, 4.0 Hz, 1H), 7.10 (d, 4.6 Hz, 1H), 7.74 (d, 4.6 Hz, 1H)

[a] Obtained with 1−5 mM solutions in $CDCl_3$ at 20 °C. [b] *m*- and *o*-tolyl peaks overlap. [c] Acetate assumed to be the axial ligand to Zn in all Zn complexes. [d] Overlap of resonances and exchange broadening make tolyl proton region too complicated to deconvolute and assign.

had unequal intensity. This is consistent with a five-coordinate Zn(II) ion coordinated in unequal proportions to each of the two inequivalent faces of the *N*-MeOEC anion. The steric effects of the *N*-methyl substituent in [Fe(*N*-MeTTP)]$^{2+}$ do not preclude addition of an axial ligand on the same face of the porphyrin.[59]

The Zn(II) *N*-methyl-hydroporphyrin complexes are more susceptible to oxidative decomposition than the corresponding free-base compounds. This is particularly true during column chromatography. Interestingly, Zn(*N*-MeTTiBC)$^{+}$ appears to be selectively oxidized to Zn(*s-N23*-MeTTC)$^{+}$ when exposed to air.

^{1}H NMR Spectra. *N*-Alkylation of a porphyrin produces features in the ^{1}H NMR spectrum that distinguish it from an *N*-unsubstituted porphyrin, Tables 1 and 2. The *N*-methyl resonance appears about 4 ppm upfield from TMS because the methyl group is situated above the center of the macrocycle and thus is shielded by the ring current. The decrease from 4-fold to 2-fold symmetry splits the *meso*-tolyl-*p*-CH_3 and pyrrole β-H resonances of H(*N*-MeTTP) and the *meso*-C-H and β-ethyl CH_2 and CH_3 resonances of H_2(*N*-MeOEP)$^{+}$. The change in the H(*N*-MeTTP) pyrrole β-H shifts is substantial and suggests that *N*-substitution has a significant electronic effect. Singlets are observed for the magnetically equivalent protons of the *N*-substituted pyrrole ring and of the opposite pyrrole ring. A pair of doublets are observed for the inequivalent protons of the adjacent pyrrole rings. Particularly noteworthy is the nearly 1.5 ppm upfield shift of one of the pyrrole β-H singlets from its position in the *N*-unsubstituted compound. This singlet was assigned tentatively to the *N*-substituted pyrrole ring.[9] The other pyrrole β-H resonances shift by less than 0.40 ppm. The appearance of the tolyl resonances, whose shift range overlaps that of the pyrrole β-H resonances, is complicated and temperature dependent. The *N*-methyl group differentiates the two faces of the macrocycle. Thus, *ortho*- and *meso*- protons on opposite sides of each tolyl ring are magnetically inequivalent. If rotation is restricted, the tolyl ring will generate an eight line AA′BB′ subspectrum (assuming that the smaller *meta* and *para* couplings are not resolved). At fast rates of rotation, chemical exchange collapses this to a four line AB subspectrum. The spectrum of H(*N*-MeTTP) at 20 °C establishes that tolyl ring rotation is restricted and that rate of chemical exchange is intermediate. Nine broad lines with quite different line widths are observed for the two inequivalent tolyl sites. Another example of chemical exchange phenomenon resulting from restricted meso aryl ring rotation in *N*-substituted porphyrins was reported recently for the cationic-periphery porphyrin *N*-methyltetrakis(*p*-(aminomethyl)phenyl)porphyrin.[76] In the presence of water or trace acidic impurities, chemical exchange between neutral H(*N*-MeTTP) and its protonated cation can lead to broadened lines. The N−H resonance typically is not

(76) Lavallee, D. K.; Xu, Z.; Pina, R. *J. Org. Chem.* **1993**, *58*, 6000−6008.

Table 2. ^{1}H NMR Data for N-Methyl-octaethylhydroporphyrins[a]

position	H_2(*N*−MeOEC)$^+$ [b]	Zn(*N*−MeOEC)$^+$ [c]	position	H_2(*N*−MeOEiBC)$^+$ [b]
N-CH_3	−3.823 (s, 3H)	−3.01 (s, 3H, maj[d]), −3.02 (s, min)	*N*−CH_3	−2.510, −2.523, −2.553
N-H	−3.77 (br s, 1H), −3.69 (br s, 1H)		5−H	7.646 (s, ttt[e,f]), 7.655 (s, ttt[f]),
2-CH_3	1.028 (t, 3H)	1.18 (t, 6H)		7.565 (s, tct[g]), 7.591 (s, tct)
3-CH_3	1.267 (t, 3H)		10,20−H	7.909 (s, ttt), 7.976 (s, ttt), 7.872 (s, tct),
7,18-CH_3	1.857 (t, 6H)	1.78 (t, 12H)		7.888 (s, tct), 8.041 (tct[h])
8,17-CH_3	1.853 (t, 6H)			
12,13-CH_3	1.427 (t, 3H), 1.439 (t, 3H)	1.52 (t, 3H), 1.60 (t, 3H)	15−H	8.907 (s, ttt), 8.890 (tct[h])
2-CH_2[i]	1.99 (m, 1H), 2.31 (m, 1H)	1.95 (m, 1H), 2.20 (m, 1H)		
3-CH_2[i]	2.31 (m, 1H), 2.63 (m, 1H)	2.20 (m, 1H), 2.42 (m, 1H),		
7,18-CH_2	3.92 (q, 4H)			
8,17-CH_2	4.04 (q, 4H)	3.55−3.80 (m, 12H)		
12,13-CH_2	3.72 (m, 2H), 3.81 (m, 2H)			
2-H	4.71 (m, 1H)	4.38 (m, 2H)		
3-H	4.54 (m, 1H)			
5,10-H	9.116 (s, 1H), 9.134 (s, 1H)	8.50 (s, 2H maj), 8.49 (s, min)		
15,20-H	9.917 (s, 1H), 9.930 (s, 1H)	9.42 (s, 1H, maj), 9.43 (s, 1H, maj), 9.38 (s, min), 9.40 (s, min)		

[a] Obtained with 5 mM solutions in $CDCl_3$. [b] Triflate salt. [c] Acetate salt. [d] Maj and min are the major and minor components of the mixture of diastereomers of this compound. The intensity ratio of maj/min for corresponding peaks is constant. [e] Peak due to a diastereomer formed from *ttt*-H_2(OEiBC), which was present in greater amount in the H_2(OEiBC) starting material. [f] Resolved ttt meso peaks are each half the intensity of other, unresolved *ttt* meso peaks. [g] Peak due to a diastereomer formed from *tct*-H_2(OEiBC), which was present in lesser amount in the H_2(OEiBC) starting material. [h] Peak is beginning to resolve into two lines and is twice the intensity of resolved tct meso peaks. [i] The two protons of the 2- and 3-CH_2 methylene groups are nonequivalent. One proton from each methylene group appears near 2.31 ppm in the free-base and 2.20 ppm in the Zn(II) complex.

observed at room temperature, even in purified and dried solvents. This could also be a result of tautomeric exchange.

The NMR spectra of *N*-substituted hydroporphyrins retain the characteristics of both *N*-substituted porphyrins and hydroporphyrins, but the lower symmetry makes the spectra even more complicated. In most cases, all of the magnetically inequivalent groups of protons can either be individually resolved or are apparent from their effects on multiplets. The *N*-methyl singlets remain upfield of TMS, but the shifts become less negative with increasing saturation of the hydroporphyrin. The dispersion of these resonances is sufficiently large that the shift readily identifies both the macrocycle reduction level and the individual isomer. The shifts are more negative for the corresponding *N*-methyl octaethyl hydroporphyrin cations due both to the effects of β-octaalkyl- vs *meso*-tetraaryl-substitution and to an upfield shift of the *N*-alkyl resonance that occurs upon protonation of the neutral macrocycle.[9] The decreased ring current in the *N*-methyl hydroporphyrins relative to *N*-methyl porphyrin also is evident in the upfield shifts of the pyrrole β-H and tolyl *o*-H and *p*-CH_3 resonances of the *meso*-tetratolyl compounds and the upfield shifts of the *meso*-CH resonances of the octaethyl compounds.

Coordination of *N*-substituted porphyrin compounds to Zn(II) results in downfield shifts of the *N*-methyl resonance by about 0.3 ppm or less, of the unique upfield pyrrole β-H singlet of *meso*-tetraarylporphyrins by about 0.8−1.1 ppm, and of the *meso*-CH resonances of octaethylporphyrins by roughly 0.3−0.4 ppm.[9] Hydroporphyrin *N*-methyl resonances experience much larger downfield shifts: between 0.5 and 0.6 ppm for the neutral *meso*-tetratolylchlorins, 0.82 ppm for the protonated H_2(*s*-*N23*-MeOEC)$^+$ cation, and 1.3 ppm for the neutral H(*N*-MeTTiBC). Although the six pyrrole β-H doublets of free-base- and of Zn(*u*-*N22*-MeTTC)$^+$ can neither be directly correlated nor assigned to specific positions, the ranges of chemical shifts for these compounds require that two doublets move downfield by at least 1.0−1.5 ppm. In contrast, the magnitude of change in pyrrole β-H chemical shift upon metalation of H(*s*-*N23*-MeTTC) and H(*N*-MeTTiBC) are much smaller. At least one H(*N*-MeTTiBC) pyrrole β-H doublet moves upfield. Similarly, the *meso*-CH resonances of H_2(*s*-*N23*-MeOEC)$^+$ shifts upfield in the Zn(II) complex.

The NMR data unequivocally establish the isomeric structures of several of the compounds and are suggestive of the structures of the others. The only possible structure for H(*u*-*N22*-MeTTC) is the unsymmetrical chlorin isomer. The shift ranges of the *N*-methyl and the pyrrole β-H resonances and the multiplet centered near 4 ppm that integrates to four protons establish that the compound is a chlorin. The six pyrrole β-H doublets show the compound lacks symmetry. The spectrum of H(*s*-*N23*-MeTTC) establishes that it is a chlorin with 2-fold symmetry. If the assignment criterion for *N*-substituted porphyrins of an upfield shift of the β-H resonances of the methylated pyrrole ring also applies to hydroporphyrins, methylation in H(*s*-*N23*-MeTTC) has occurred at N(23) rather than N(21). This criterion was applied previously to suggest that *N*-MeOEC is methylated at N(23) given the upfield shifts of the resonances of two of the six pyrrole ethyl groups.[55] The criterion appears to apply to *meso*-tetraarylchlorins. The pyrrole β-H singlet of H(*s*-*N23*-MeTTC) shifts upfield by 1.3 ppm relative to its position in H_2(TTC) and only relatively smaller changes occur in the shifts of the pyrroline β-H multiplets. In addition, two of the pyrrole β-H doublets of H(*u*-*N22*-MeTTC) shift upfield by 1.1−1.3 ppm. However, three pyrrole β-H doublets of H(*N*-MeTTiBC) shift upfield by only 0.22 ppm or less, and one shifts downfield by 0.53 ppm. (This assumes the doublets at 7.31 and 7.92 ppm correspond to protons 2 and 8.) It is possible that saturation to the level of an isobacteriochlorin diminshes the ring current sufficiently that the structural distortions introduced by *N*-substitution no longer cause much change in the deshielding experienced by pyrrole ring substituents. A second alternative, which we consider unlikely, is that H(*N*-MeTTiBC) is methylated on a pyrroline ring, i.e., N(21). If the selectivity for direct methylation of H_2(TTiBC) and of H_2(OEiBC) are the same, as is suggested by the UV−vis spectra of these compounds (below) and appears to be the case for H_2(TTC) and H_2(OEC), the NMR spectrum of H_2(*N*-MeOEiBC)$^+$ would rule out this alternative. Two of the four pyrrole ethyl resonances of OEiBC shift upfield upon methylation. The complexity of the resonances of the diastereotopic CH_2 protons of these shifted ethyl groups also is consistent with methylation on the adjacent pyrrole nitrogen atom. (The data for these resonances are not reported in Table 2 because the presence of

Table 3. Absorption Spectral Data for *N*-Methyl Hydroporphyrin and Related Compounds[a]

compound	λ_{max}, nm (ϵ, mM or relative A)[b]
H_2(TTP)	420 (382), 515 (16.9), 550 (9.1), 592 (5.0), 647 (4.2)
H_2(TTC)	420 (166), 521 (16.7), 547 (11.5), 597 (6.0), 653 (32.6)
H_2(TTiBC)	373 (53.8), 392 (80.4), 408 (56.9), 515 (8.7), 550 (14.7), 593 (20.3)
H_2(TTBC)	356 (82.9), 368 (83.0), 378 (101), 523 (38.2), 740 (79.1)
H(*N*-MeTTP)	435 (268), 533 (8.9), 575 (15.6), 617 (4.9), 679 (5.6)
H(*s-N23*-MeTTC)	437 (72.8), 457sh[c],554 (7.0), 583 (7.6), 630 (4.6), 681 (2.9)
H(*u-N22*-MeTTC)	423 (92.7), 538sh (16.3), 568 (7.0), 614 (12.9), 668 (9.2)
H(*N*-MeTTiBC)	389 (62.2), 411 (80.2), 558 (13.3), 622 (9.3), 673 (14.3)
Zn(*N*-MeTTP)(OAc)	330 (0.15), 440 (1.00), 450sh (0.96), 530sh (0.032), 562 (0.055), 615 (0.088), 661 (0.053)
Zn(*s-N23*-MeTTC)(OAc)	438 (1.00), 463 (0.67), 567 (0.12), 643 (0.15)
Zn(*u-N22*-MeTTC)(OAc)	424sh (0.56), 442 (1.00), 549 (0.06), 625 (0.12), 667 (0.21)
Zn(*N*-MeTTiBC)(OAc)	402 (0.55), 421 (1.00), 444 (0.51), 537−655 broad (0.14)
H_2(*s-N23*-MeOEC)(CF_3SO_3)	397 (1.00), 414 (0.88), 533 (0.059), 552 (0.060), 621 (0.11), 656sh (0.023)
Zn(*s-N23*-MeOEC)(OAc)	345 (0.29), 405sh (0.80), 415sh (0.91), 425 (1.00), 521 (0.072), 592 (0.088), 621 (0.12)
H(*N*-MeOEiBC)	376 (1.00), 385sh, 404 (0.87), 484 (0.08), 526 (0.09), 597 (0.07), 653 (0.29)
H_2(N-MeOEiBC)(CF_3SO_3)	369 (0.57), 388 (0.53), 409 (1.00), 493 (0.09), 522 (0.07), 588 (0.12), 632 (0.38)

[a] Benzene solution. [b] Relative ϵ or absorbance values are known to precision indicated; absolute values are known only to several percent. [c] Shoulder. [d] Acetate from zinc(II) acetate used in preparation assumed to be axial ligand.

multiple diasteromers of H_2(*N*-MeOEiBC)$^+$ and the low symmetry of each diastereomer results in so complicated a spectrum that only the *meso*-CH and *N*-CH_3 protons can be fully resolved and assigned.) Finally, the results discussed earlier that pertain to oxidation of H(*N*-MeTTiBC) to isomeric chlorins are consistent with pyrrole methylation.

NOE difference and COSY spectra were obtained to confirm these structural assignments. Irradiation of the *N*-methyl group of H(*s-N23*-MeTTC) or of H(*N*-MeTTiBC) failed to produce any observable NOE effect. If the *N*-methyl group is on N(21) in the pyrroline ring, one would expect to observe an NOE between the methyl group and the pyrroline β-protons that are on the same side of the macrocycle. NOE experiments confirmed that H_2(*s-N23*-MeOEC)$^+$ has the methyl group on the pyrrole ring opposite the pyrroline ring. Irradiation of the *N*-methyl group produced a strong NOE effect on the 10,15−*meso* protons at 9.926 ppm but none on the pyrroline β-protons. Irradiation of the pyrroline β-protons produced a strong NOE on the 5,15-*meso* protons at 9.125 ppm. The reverse experiments gave complementary results. Additional experiments afforded the complete assignment of the spectrum, Table 2.

The aromatic region of spectra of the *N*-methyl-*meso*-tetratolyl compounds has a complicated and variable appearance due to chemical exchange of the magnetically inequivalent sides of each tolyl ring. Individual exchange-related proton sets achieve coalescence at different temperatures because the frequency differences between the various exchange-related *ortho* and *meta* protons on the these tolyl rings are different. Moreover, the barriers to rotation of the several symmetry differentiated tolyl rings may be different. Both sets of *meta* protons of H(*N*-MeTTP) are well above coalescence at 20 °C. In contrast, the downfield *ortho* proton set is only near coalescence and the upfield *ortho* proton set is below coalescence. At the same temperature, the spectrum of H(*s-N23*-MeTTC) shows the *meta* and downfield *ortho* proton sets well above coalescence and the upfield *ortho* proton set near coalescence. The presence of three and four different tolyl rings in H(*N*-MeTTiBC) and H(*u-N*-MeTTC), respectively, make their spectra too complicated to deconvolute. However, they also appear to be much nearer the fast exchange limit than H(*N*-MeTTP). The Zn(II) complexes of the *N*-methyl-*meso*-tetratolyl compounds all have spectra that are nearer the slow exchange limit. The *meta* proton sets of Zn(*N*-MeTTP)$^+$ are just at coalescence at 20 °C, and each of the four *ortho* protons exhibit a single broad line. Without a detailed study of these systems, it is not clear whether the faster exchange in the hydroporphyrin compounds and slower exchange in the Zn(II) complexes reflect differences in the rotation rates (i.e., barriers) or merely smaller frequency differences between the exchanging protons. Estimation of individual proton shifts at temperatures near the slow exchange limit suggest it is the former. Clearly, though, the barrier to aryl ring rotation is markedly lower in the *N*-substituted compounds than in *N*-unsubstituted tetraarylporphyrins like TiO(TTP), In(TTP)Cl, and Ru(CO)(TTP).[77] The lower barrier may be a consequence of the canting of the *N*-substituted pyrrole ring out of the porphyrin plane. Figure 2 shows that this distortion allows the adjacent tolyl rings of H(*u-N22*-MeTTC) to assume a shallower angle than typically seen in structures of *meso*-tetraarylporphyrins.

Absorption Spectra. The absorption bands of *N*-methyl porphyrins and hydroporphyrins, Table 3, are significantly red-shifted and broadened compared to the bands of the corresponding *N*-unsubstituted compounds. The Soret region exhibits prominent shoulders or partial resolved bands, which implies that two or more distinct transitions occur. The visible bands are exceedingly broad and poorly resolved. Thus, the maxima of the bands are ill defined and appear to show substantial solvent-induced shifts in their positions.

The spectra of the isomeric *N*-methyl chlorins H(*s-N23*-MeTTC) and H(*u-N22*-MeTTC) show that the difference in the position of the *N*-methyl group causes major structural and/or electronic differences. The Soret and longest wavelength visible band of the unsymmetric chlorin is blue-shifted by roughly 13 nm relative to the symmetric chlorin. In addition, the individual visible bands of the unsymmetric chlorin are better resolved.

The relative intensities and band shapes in the spectra of H_2(*s-N23*-MeOEC)$^+$ and H_2(*N*-MeOEiBC)$^+$ are strikingly similar to those in the spectra of H_3(OEC)$^+$ and H_3(OEiBC)$^+$, respectively.[42,78,79] However, the positions of the *N*-methyl hydroporphyrin bands are red-shifted by roughly 5 nm. The spectrum of H_2(*s-N23*-MeOEC)$^+$ is in good agreement with spectrum reported for the fluorosulfonate salt.[55] The neutral compound H(*N*-MeOEiBC) can be obtained in the presence of an appropriate base. The spectrum of the compound resembles that of H(*N*-MeTTiBC), especially in sharing the feature of a prominent band at longer wavelength (>650 nm), but is blue-shifted by 10−20 nm with respect to the latter. The similarity in the appearance of the spectra suggests that the site of methylation is the same in these two compounds.

Voltammetry. Cyclic voltammetry was used to examine the

(77) Eaton, S. S.; Eaton, G. R. *J. Am. Chem. Soc.* **1977**, *99*, 6594−6599.
(78) Fuhrhop, J.-H. *Z. Naturforsch. B* **1970**, *25*, 255.
(79) Stolzenberg, A. M. Ph. D. Thesis, Stanford University, 1980.

Table 4. Potentials of Free-Base and Zn(II) Complexes of *N*-Methyl-*meso*-Tetratolyl-Porphyrins and Hydroporphyrins

	$E_{1/2}$,[a] V[b]				
compound	2+/1+	1+/0	0/1−	1− /2−	other
H_2(TTP)	1.13	0.91	−1.28	−1.62	
H_2(TTC)	0.98	0.74	−1.32	−1.68	−1.85[c]
H_2(TTiBC)	0.89	0.49	−1.57		
H_2(TTBC)		0.39	−1.34		
H(*N*-MeTTP)	1.10	0.70	−1.30	−1.63[c,d]	1.41,[d,e] −1.47, −0.93[d−f]
H(*s-N23*-MeTTC)	1.09[d,e]	0.75[d,e]	−0.73[g]	−1.33[c,d]	1.38,[d,e] −1.61,[c,d]
H(*u-N22*-MeTTC)	1.09[d,e]	0.68[d,e]	−1.34[c,d]	−1.61[c,d]	
H(*N*-MeTTiBC)	0.92[d,e]	0.47[d,e]	−1.16[c,d]	−1.59[c,d]	
Zn(*N*-MeTTP)(OAc)	1.26[d,e]	0.91	−1.08	−1.44	1.41[d,e]
Zn(*s-N23*-MeTTC)(OAc)	1.09[d,e]	0.90[d,e]	−1.12	−1.44	
Zn(*N*-MeTTiBC)(OAc)		0.63[d,e]	−1.36		

[a] $E_{1/2} = 0.5(E_{p,a} + E_{p,c})$. [b] Vs SCE at 25 °C in methylene chloride solution 0.1 M in TBAP. [c] $E_{p,c}$ (irreversible). [d] Peak position at 100 mV/s scan rate. [e] $E_{p,a}$ (irreversible). [f] Both peaks appear after scanning −1.63 V peak. [g] At slower scan rates, new anodic peak grows at −0.38 V after scanning this process.

redox processes of free-base and Zn(II) complexes of *N*-methyl-*meso*-tetratolylporphyrins and -hydroporphyrins in methylene chloride solution. Potential data are collected in Table 4. Data for free-base *meso*-tetratolylporphyrin and -hydroporphyrins are included for purposes of comparison.

The cyclic voltammograms of the *N*-unsubstituted compounds generally exhibit two one-electron oxidations and two one-electron reductions within the accessible potential range. The processes are chemical reversible ($i_{p,a} = i_{p,c}$) on the cyclic voltammetric time scale at a scan rate of 100 mV/s. However, the larger than theoretical peak-to-peak separations suggest that the processes are not strictly reversible in the sense of maintaining the Nernstian equilibrium at the electrode. The potentials follow similar trends to those observed previously for other hydroporphyrin compounds.

The most notable feature of the voltammograms of the free-base and Zn(II) complexes of *N*-methyl-*meso*-tetratolylhydroporphyrins is the near total irreversibility of most redox processes. In contrast, the redox processes of H(*N*-MeTTP) and Zn(*N*-MeTTP)$^+$ are reversible. The *N*-methyl hydroporphyrin oxidation processes exhibit neither an associated cathodic peak nor a cathodic peak that results from an ECE process. H(*N*-MeTTC) is the only free-base *N*-methyl hydroporphyrin compound that exhibits as much as a quasi-reversible reduction on the cyclic voltammetric time scale. Scanning through its reduction at −0.73 V results in the appearance of a new, small anodic peak at −0.38 V. In contrast, the first reductions of the Zn(II) complexes are chemically reversible. Subsequent reductions exhibit new anodic peaks that appear to result from ECE processes. The irreversibility of the majority of the *N*-methyl hydroporphyrin redox processes suggest that these compounds undergo major structural changes upon oxidation or reduction and consequently have slow electron transfer kinetics.

The potentials reported in Table 3 for the *N*-methyl hydroporphyrin compounds are peak potentials rather than $E_{1/2}$s and must therefore be at least 30 mV positive of the $E_{1/2}$. Although a direct comparison of thermodynamic potentials of *N*-methyl substituted and *N*-unsubstituted compounds is not possible, it is nonetheless clear from the data that *N*-methylation of a porphyrin or hydroporphyrin must decrease the potential of its oxidation. Moreover, coordination of Zn(II) increases the potential of the oxidation of an *N*-methyl substituted compound.

Summary and Conclusions

The principal results and conclusions of this investigation are listed below.

(1) Several free-base and Zn(II) *N*-methyl substituted chlorin and isobacteriochlorin complexes were synthesized and characterized.

(2) Direct methylation of free-base hydroporphyrins is unexpectedly selective. Only one possible regioisomer is produced. This result appears to be independent of the identities of the electrophilic reagent or the peripheral substituents on the hydroporphyrin.

(3) Methylation occurs on a pyrrole ring rather than a pyrroline ring. In chlorins, the pyrrole ring opposite the pyrroline ring is methylated to afford the symmetric *N*-methyl chlorins H(*s-N23*-MeTTC) and H_2(*s-N23*-MeOEC)$^+$.

(4) The selectivity is a result of kinetic rather than thermodynamic factors. Slow reoxidation of H(*N*-MeTTiBC) affords the unsymmetric *N*-methyl chlorin H(*u-N22*-MeTTC).

(5) Bacteriochlorins are not methylated by any of the electrophilic reagents investigated.

(6) Reduction of H(*N*-MeTTP) with *p*-toluenesulfonhydrazide affords a mixture of compounds that contains the unsymmetrical *N*-methyl chlorin H(*u-N22*-MeTTC) and another yet unidentified *N*-methyl hydroporphyrin. The selectivity of this reaction appears to be complementary to the direct methylation of free-base hydroporphyrins.

(7) The electronic effects of aryl substituents in *meso*-tetraarylporphyrins alter the rates of reduction, both relative and absolute, to the various hydroporphyrins by *p*-toluenesulfonhydrazide.

The selectivity of the alkylation of chlorin and isobacteriochlorin and the inertness of the bacteriochlorin to alkylation stand in striking contrast to the reactivity of unsymmetrically substituted porphyrins. One possible rationalization of the differences in reactivity centers on the effects of the lowered symmetry on the equilibria of the NH tautomers. Unsymmetrical substitution of a porphyrin might not affect significantly the relative populations of the two preferred trans tautomers (i.e., 21-H,23-H and 22-H,24-H), which are degenerate in symmetrical porphyrins. The four pyrrole nitrogen atoms would be unprotonated and available to react with electrophiles to a similar extent. However, the lower symmetry of the π-system in hydroporphyrins could both greatly favor one tautomer over others and raise the activation barrier to interconversion of tautomers. The two unprotonated nitrogen atoms in the preferred tautomer might also be differentiated electronically by the lowered symmetry of the π-system. We are currently testing the validity of these ideas.

Experimental Section

All reactions, chromatography, recrystallizations, and sample manipulations involving hydroporphyrins were carried out under a nitrogen atmosphere using standard Schlenk techniques or in a Vacuum/Atmospheres Co. Drybox, unless otherwise noted. Reagents and solvents used in this study were HPLC or reagent grade. Solvents were

dried by appropriate methods and thoroughly degassed prior to use. NMR solvents were treated to remove traces of water and acid immediately before use by passage down a dry column of grade I basic alumina. The initial runnings were discarded. The *meso*-tetraarylporphyrins H_2(TPP), H_2(TTP), H_2(TXP), H_2(T*p*NO_2PP), and H_2(T*p*FPP) were prepared from pyrrole and the appropriate substituted benzaldehyde by the Adler-Longo method.[80] H_2(OEP),[81] *t*-H_2(OEC),[42] H_2(OEiBC),[42] and [$MeSPh_2$][BF_4][59] were prepared by literature methods. Absorption spectra were recorded on a Perkin-Elmer Lambda 6 UV−vis spectrophotometer. ^{1}H NMR spectra were recorded on a JEOL Eclipse 270 spectrometer (270.17 M Hz) or a Varian Gemini 300 broadband spectrometer (300.075 M Hz) at 20°C. Electrochemical measurements were obtained as before.[82]

H_2(TTC). A mixture of 1.0 g (1.49 mmol) of H_2(TTP), 4.0 g (28.9 mmol) of anhydrous K_2CO_3, 4.0 g (21.5 mmol) of *p*-toluenesulfonhydrazide, and 250 mL of dry pyridine (distilled from BaO) was placed in a 500 mL three-neck flask that was equipped with a gas inlet atop a reflux condensor, a septum, a stir bar, and a thermocouple probe connected to a J-Kem model 210T temperature controller. The contents of the flask were degassed and placed under nitrogen. The solution was heated and stirred at 100 °C overnight. The reaction mixture was monitored by UV−vis or ^{1}H NMR spectroscopy. After the overnight period, additional aliquots of *p*-toluenesulfonhydrazide (2.0 g in 10 mL of pyridine) were added to the reaction mixture every 3 h, if necessary, until H_2(TTP) was consumed. At this point the reaction mixture usually contained about 15% H_2(TTBC). The mixture was then cooled to room temperature, diluted with chloroform (200 mL), and washed in a separatory funnel with water (2 × 100 mL), cold 3 N HCl (100 mL), water (2 × 100 mL), and a saturated aqueous solution of sodium bicarbonate (100 mL). The chloroform solvent was removed on a rotary evaporator, and the residue was dried under vacuum to afford 0.8 g (80% yield) of a purple solid that was typically 80−90% pure H_2(TTC). The solid can be purified as described below or used as isolated in the synthesis of H(*N*-MeTTC).

H_2(TTBC). The compound was prepared by a modification of synthetic procedure of H_2(TTC). After an initial heating period of 4 h, additional aliquots of *p*-toluenesulfonhydrazide (1.0 g in 5 mL of pyridine) were added every 4 h (except for one addition during the night) until the UV−vis spectrum indicated the conversion of H_2(TTC) to H_2(TTBC) was approximately 80% complete. This typically took 36−48 h. Further reaction results in loss of product due to increased production of hexahydroporphyrins. The reaction mixture was worked up as before to afford 0.75 g (75% yield) of a reddish purple solid. Purification of the solid, described below, resulted in great loss of material. Only about 0.10 g of pure H_2(TTBC) was recovered from the 0.75 g sample.

H_2TTiBC. A mixture of 1.0 g (1.49 mmol) of H_2(TTP), 1.0 g (4.5 mmol) $Zn(OAc)_2 \cdot 2H_2O$, and 75 mL of pyridine was placed in a 250 mL three-neck flask that was equipped as in the preparation of H_2(TTC). The mixture was degassed, heated to reflux for 1 h to form Zn(TTP), and allowed to cool to room temperature. Anhydrous K_2CO_3 (4.0 g) and 6.0 g (32.2 mmol) *p*-toluenesulfonhydrazide were added to the flask under nitrogen. The mixture was heated to 100 °C for 36 h. Aliquots of *p*-toluenesulfonhydrazide (4.0 g in 10 mL of pyridine) were added every 6 h. The mixture was cooled to room temperature, and 200 mL of chloroform was added. The solution was washed in a separatory funnel with water (2 × 100 mL), cold 3 N HCl (100 mL), cold concentrated HCl (to remove the zinc), water (2 × 100 mL), and a saturated solution of sodium bicarbonate (100 mL). The chloroform solvent was removed on a rotary evaporator, and and the residue was dried under vacuum to afford 0.82 g (82% yield) of a purple solid that was roughly 85% pure H_2(TTiBC). The solid can be purified as described below or used as isolated in the synthesis of H(*N*-MeTTiBC).

Purification of Tetratolylhydroporphyrins. A 0.5 g sample of impure hydroporphyrin was dissolved in a minimal quantity of degassed 1:1 methylene chloride/hexane. The resulting solution was applied to a 6 × 50 cm flash silica column that had been slurry packed under nitrogen with the same solvent mixture. Elution with 1:1 methylene chloride/hexane initially gave a band of H_2(TTBC), which can appear green or pink in color depending upon its concentration. A large red band eluted soon thereafter. The front of the red band is pure H_2(TTC), but the tail of the band can also contain H_2(TTP). A bright reddish-purple band of H_2(TTiBC) remained at the top of the column. Chloroform was used to quickly elute any residues of H_2(TTP), H_2(TTC), or H_2(TTBC). A 1:1 mixture of chloroform/ethyl acetate was then used to elute the H_2(TTiBC). The eluate from the column was collected with a fraction collector, and the purity of individual fractions was examined by UV−vis spectroscopy. The pure fractions that contained a particular compound were combined, the solvent was removed with a rotary evaporator, and the resulting solid was dried under vacuum.

H(*N*-MeTTP). H_2(TTP) (0.20 g, 0.30 mmol), 0.18 g (0.59 mmol) of [$MeSPh_2$][BF_4], and 75 mL of 1,2-dichlorobenzene were placed in a 250 mL three-neck flask that was equipped with a gas inlet atop a reflux condensor, a septum, a stir bar, and a thermocouple probe connected to a J-Kem model 210T temperature controller. The solution was freeze−pump−thaw degassed twice, stirring was initiated, and the solution was heated to 130 °C for 18 h. The resulting green solution was cooled and washed in a separtory funnel with concentrated aqueous ammonia (50 mL) and water (100 mL). The solution was applied to a 3 × 50 cm column that had been packed with a slurry of activated, grade I basic alumina in methylene chloride. A red band of unreacted H_2(TTP) began to elute from the column, leaving a green band of H(*N*-MeTTP) at the top of the column. Elution with methylene chloride continued until all of the unreacted H_2(TTP) was removed from the column. The H(*N*-MeTTP) was eluted with chloroform. The chloroform was removed on a rotary evaporator, and the residue dried under vacuum to afford 0.15 g (73% yield) of H(*N*-MeTTP) as a purple solid. The unreacted H_2(TTP) can be recovered from the column eluate by removing the 1,2-dichlorobenzene and methylene chloride under vacuum at 80 °C.

H(*s-N23*-MeTTC). The compound was prepared by the same procedure as for H(*N*-MeTTP) from either 0.2 g of pure H_2(TTC) or 0.2 g of the hydroporphyrin mixture that is 80−90% pure H_2(TTC). After workup, the green solution was applied to a 3 × 50 cm column that had been packed with a slurry of deactivated, grade III basic alumina in methylene chloride. A red band of unreacted starting materials moved down the column and was followed by a green band of H(*N*-MeTTP). A dark green band of H(*s-N23*-MeTTC) remained at the top of the column. Elution with methylene chloride was continued until all of the free-base compounds and H(*N*-MeTTP) eluted from the column. A 10:1 mixture of chloroform/ethyl acetate was used to elute the H(*s-N23*-MeTTC). The solvent mixture was removed on a rotary evaporator, and the residue dried under vacuum to afford 0.090 g (44% yield) of H(*s-N23*-MeTTC) as a greenish purple solid. The unreacted starting material was recovered as above.

H(*N*-MeTTiBC). The compound was prepared by the same procedure as for H(*N*-MeTTP) from either 0.2 g of pure H_2(TTiBC) or 0.2 g of the hydroporphyrin mixture that is predominantly H_2(TTiBC). The reaction was heated for 12 h to afford a green solution that was worked up as above. The solution was applied to a 3 × 50 cm column that had been packed with a slurry of deactivated, grade III basic alumina in methylene chloride. A red band of unreacted starting materials moved down the column and was followed by a green band of H(*N*-MeTTP). Continued elution with methylene chloride removed these bands and lead to the slow elution of a blue band of H(*N*-MeTTiBC). Addition of chloroform (10% v/v) to the methylene chloride increased the rate of elution of the blue band. A small dark green band of H(s-N23-MeTTC) remained behind on the column. The solvent mixture of the blue solution was removed on a rotary evaporator, and the residue dried under vacuum to afford 0.080 g (39% yield) of H(*N*-MeTTiBC) as a dark blue solid.

H(*u-N22*-MeTTC). Crystals of H(*u-N22*-MeTTC) were obtained serendipitously during an attempt to recrystallize H(*N*-MeTTiBC). A sample of H(*N*-MeTTiBC) was dissolved in a minimal quantity of methylene chloride, and a layer of hexane was carefully placed on top of the methylene chloride solution without causing the two phases to mix. Dark crystals of H(*u-N22*-MeTTC) formed upon standing,

(80) Adler, A. D.; Longo, F. R.; Finarelli, J. D.; Goldmacher, J.; Assour, J.; Korsakoff, L. *J. Org. Chem.* **1967**, *32*, 476.

(81) Sessler, J. L.; Mozaffari, A.; Johnson, M. R. *Org. Synth.* **1992**, *70*, 68−78.

(82) Stolzenberg, A. M.; Glazer, P. A.; Foxman, B. M. *Inorg. Chem.* **1986**, *25*, 983−991.

ostensibly under nitrogen. Exposure of solutions of H(*N*-MeTTiBC) to air also results in formation of H(*u*-*N22*-MeTTC).

Preparation of *N*-Methyloctaethylhydroporphyrin Compounds. The procedure for the synthesis of $[H_2(s\text{-}N23\text{-MeOEC})][CF_3SO_3]$ is typical. Methyl trifluoromethanesulfonate (1.0 g, 6.1 mmol) was added to a solution of 0.20 g (0.37 mmol) of H_2(OEC) in methylene chloride. The color of the solution immediately changed from green to violet. The solution was stirred at room temperature for 24 h. Evaporation of the solution afforded a residue which was dissolved in chloroform and purified by chromatography on a column of grade III neutral alumina. Elution with chloroform gave a green band of unreacted H_2(OEC). Elution with 10:1 chloroform/methanol gave a blue-violet band of the product. Evaporation of the solvent and recrystallization of the residue afforded 0.11 g (42% yield) of $[H_2(s\text{-}N23\text{-MeOEC})][CF_3SO_3]$.

Preparation of Zn(II)−*N*-Methylhydroporphyrin Complexes. Metalation with zinc can be conducted in several solvent systems with a variety of Zn(II) salts. A typical procedure for *N*-methyl porphyrins and chlorins is given below. The procedure for *N*-methylisobacteriochlorins used equal weights of free-base and zinc salt, omitted the water wash, and used a tituration of the solid residue with diethyl ether to separate the complex and excess zinc salt.

The free-base *N*-methyl hydroporphyrin compound (0.60 g) was dissolved in 30 mL of degassed benzene, and 0.10 g of $Zn(OAc)_2 \cdot 2H_2O$ was added. The reaction mixture was stirred for 1 h, during which time the color became a more intense green. The mixture was washed with degassed water (2×50 mL) and dried over $MgSO_4$, and the solvent evaporated under vacuum to afford a green solid. Chromatography on grade III neutral alumina results in some loss of complex through decomposition and no improvement in purity.

Acknowledgment. We thank Professor Jeffrey L. Petersen of the WVU Chemistry Department for assistance with the X-ray structure of H(*u*-*N22*-MeTTC) and Professor Peter M. Gannett of the WVU School of Pharmacy for assistance with NOE experiments. This research was supported by the Donors of the Petroleum Research Fund, administered by the American Chemical Society (Grant ACS-PRF No. 23351-AC3) and by the National Institutes of Health (Grant GM-33882).

JA972210Q