Synthesis and Characterization of Blocked and Ligand-Appended Hemes Derived from Atropisomeric *meso*-Diphenylporphyrins

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Abstract: The synthesis of a series of sterically blocked and imidazole-appended *meso*-diphenyletioporphyrins is described. These hybrid porphyrins have good solubility and spectroscopic properties of β-substituted porphyrins as well as the orientation specificity of ortho-position-derivatized tetraphenylporphyrins. The effectiveness of the blocking groups is demonstrated by ferric hemin hydroxide formation in the doubly protected *trans*-5,15-bis[*o*-(*p*-*tert*-butylbenzamido)phenyl]-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphine, characterized by UV–visible, ^{1}H NMR, and IR spectra and cyclic voltammetry. The advantage of the *m*-benzyl linkage in enforcing imidazole coordination to ferric hemes is demonstrated by ^{1}H NMR studies on various types of imidazole-appended heme complexes. Several potential binucleating systems have also been prepared by incorporating nonheme chelating ligands to the hybrid porphyrins.

The construction of synthetic metalloporphyrin complexes which mimic heme-containing proteins has been one of the most powerful methods in studying reaction mechanisms and probing structure–function relationships of hemoproteins. Most existing model systems are based on two families of porphyrins: the β-substituted porphyrins (e.g., protoporphyrin) and the meso-substituted tetraphenyl (TPP) derivatives. These two types of porphyrins have been exploited extensively in the last decade to give many interesting model compounds with colorful names.[1-4] The β-substituted compounds resemble more closely naturally occurring hemes but the excessive floppiness of side chains used in functionalization is often undesirable. The tetraphenyl system, particularly those functionalized via *o*-anilido groups (e.g., the "picket-fence" heme[3]), is structurally more rigid. Nevertheless, they suffer from the fact that synthetically it is very difficult to derivatize one particular phenyl group (out of four) on the porphyrin ring in order to attach special appendages. Recently, Gunter and Mander[5] reported a hybrid *meso*-diphenylporphyrin. This system appears to be attractive for model building purposes in that the atropisomers of the ortho-substituted derivative can be separately obtained and that each isomer may be manipulated further to yield a variety of useful heme model compounds. While the original authors described the synthesis of a heme–copper complex[5,6] based on one of the diphenylporphyrin isomers, this useful system has not been exploited in any other means. This could be, at least in part, attributable to the difficulty in obtaining the dipyrrylmethane starting material. The purpose of this paper is to demonstrate the utilization of this hybrid porphyrin as biomimetic heme models through streamlined synthesis. The diphenylporphyrins **1a** and **1b**, substituted with ethyl and methyl groups, are easier to prepare and substantially more soluble in organic solvents than the octamethyl analogues. Since free rotation of the phenyl rings in this system is hindered, such steric constraints and conformational rigidity can be employed to bring about selective ligation and/or blockage of the porphyrin coordination site. Our results demonstrate that a large number of novel penta-, and hexacoordinate heme derivatives can be generated conveniently using this approach. The application of these synthetic hemes in modelling O_2 and CO binding in hemoglobins and myoglobins is reported elsewhere.[7]

Results and Discussion

Synthesis. The parent compound, 5,15-bis(*o*-aminophenyl)-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphine, or $(NH_2)_2$-DPE (amino*di*phenyletioporphyrin II) was synthesized by condensation of equivalent amounts of 5,5′-unsubstituted dipyrrylmethane **2** and *o*-nitrobenzaldehyde followed by reduction according to Scheme I. The choice of 3,3′-diethyl-4,4′-dimethyl-2,2′-dipyrrylmethane (**2**) as starting material was not arbitrary. The prerequisite decarboxylation can be achieved very easily in one step from a diester precursor. In contrast, the tetramethyldipyrrylmethane used by Gunter and Manter[5] was notoriously difficult to prepare and a bomb reactor was needed to effect the decarboxylation. In the present scheme, the yields were better than 70% in each step. The ethyl side chains on the ring rendered **1a** and **1b** quite soluble in organic solvents so that separation of the atropisomers could be achieved in large scale by column chromatography. The ethylside chains on the ring rendered **1a** and **1b** quite soluble in organic solvents so that separation of the atropisomers could be achieved in large scale by column chromatography. The isolated atropisomers were very stable, only under prolonged heating at >100 °C could they be thermally equilibrated to a 1:1 mixture of cis:trans isomers. The activation energies needed for thermal interconversion of the two isomers were measured to be 26.2 kcal/mol for the parent aminoporphyrin and 28.0 kcal/mol for the acetamido derivative. The rigidity of the anilides should allow the attachment of specific groups held above and below the porphyrin core. These groups can serve a wide variety of functions and be readily modifiable without causing severe changes in the overall complex.

To prepare anilido derivatives, the most efficient method was the direct coupling between acid chlorides and the aminoporphyrin.

(1) "Cyclophane" and "Crowned" Porphyrins: (a) Diekmann, H.; Chang, C. K.; Traylor, T. G. *J. Am. Chem. Soc.* **1971**, *93*, 4068. (b) Chang, C. K. *J. Am. Chem. Soc.* **1977**, *99*, 2819. (c) Traylor, T. G.; Campbell, D.; Tsuchiya, S. *J. Am. Chem. Soc.* **1979**, *101*, 4748.

(2) "Capped" and "Strapped" Porphyrins": (a) Baldwin, J. E.; Almog, J.; Dyer, R. L.; Peters, M. *J. Am. Chem. Soc.* **1975**, *97*, 226. (b) Baldwin, J. E.; Crossley, M. J.; Klose, T.; O'Rear, E. A.; Peters, M. K. *Tetrahedron Lett.* **1982**, *38*, 27. (c) Battersby, A. R.; Buckley, D. G.; Hartley, S. G.; Turnbull, M. D. *J. Chem. Soc., Chem. Commun.* **1976**, 879. (d) Battersby, A. R.; Hamilton, A. D. *J. Chem. Soc., Chem. Commun.* **1980**, 117. (e) Momenteau, M.; Lavalette, D. J. *J. Chem. Soc., Chem. Commun.* **1982**, 341. (f) Ward, B.; Chang, C. K.; Wang, C. B. *J. Am. Chem. Soc.* **1981**, *103*, 5236. (g) Ogoshi, H.; Sugimoto, H.; Yoshida, Z. *Tetrahedron Lett.* **1976**, 4477.

(3) "Picket-fence" and "Pocket" Porphyrins: (a) Collman, J. P.; Gagne, R. R.; Halbert, T. R.; Marchon, J. C.; Reed, C. A. *J. Am. Chem. Soc.* **1973**, *95*, 7868. (b) Collman, J. P.; Brauman, J. I.; Doxsee, K. M.; Halbert, T. R.; Brunnenberg, E.; Linder, R. E.; LaMar, G. N.; DelGaudio, J.; Lang, G.; Spartalian, K. *J. Am. Chem. Soc.* **1980**, *102*, 4182. (c) Collman, J. P.; Brauman, J. I.; Collins, T. J.; Iverson, B. L.; Lang, G.; Pettman, R. B.; Sessler, J. L.; Walters, M. A. *J. Am. Chem. Soc.* **1983**, *105*, 3038.

(4) "Basket Handle" and "Gabled" Porphyrins: (a) Momenteau, M.; Loock, B.; Mispelter, J.; Bisagni, E. *Nouv. J. Chem.* **1979**, *3*, 77. (b) Tabushi, I.; Sasaki, T. *J. Am. Chem. Soc.* **1983**, *105*, 2901.

(5) Gunter, M. J.; Mander, L. N. *J. Org. Chem.* **1981**, *46*, 4792.

(6) Gunter, M. J.; Mander, L. N.; Murray, K. S.; Clark, P. E. *J. Am. Chem. Soc.* **1981**, *103*, 6784.

(7) Chang, C. K. et al., manuscript submitted.

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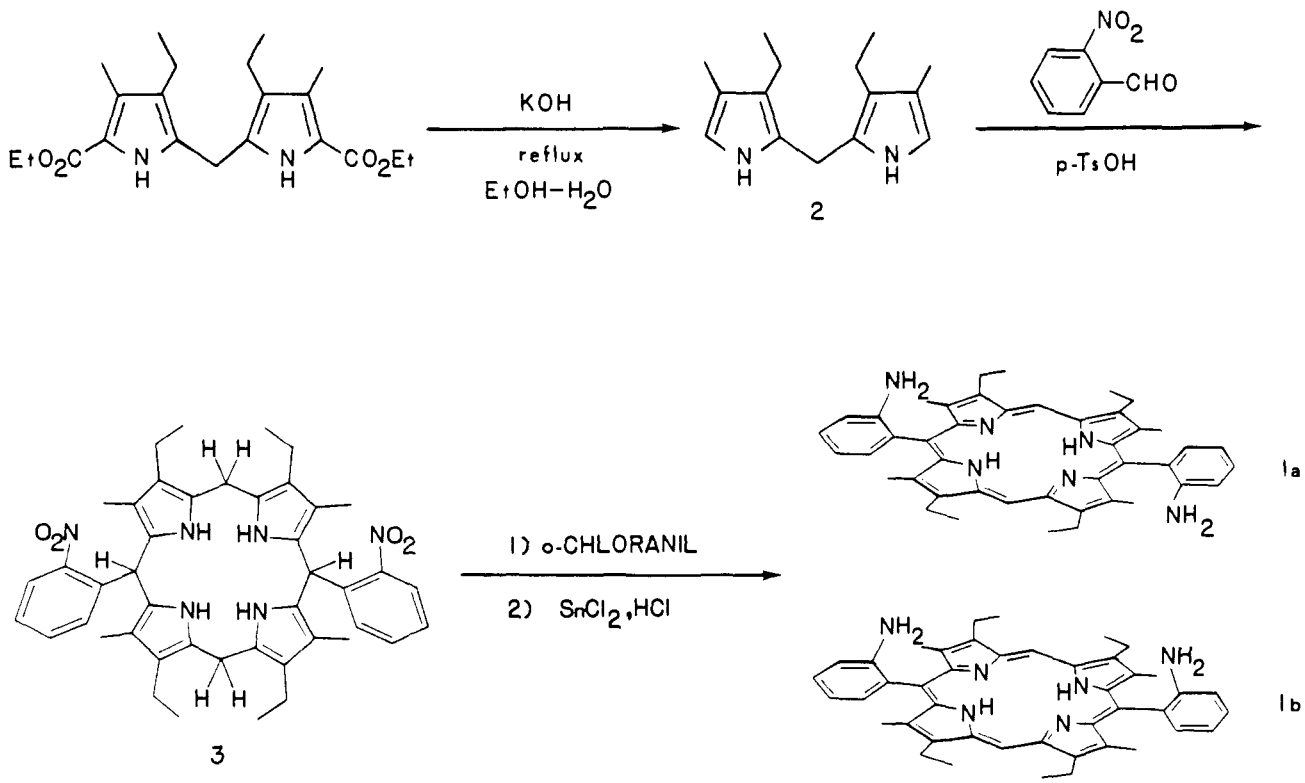
Scheme I



The yields were routinely >60% when the acid chloride could be isolated. In cases where the acid chloride could not be isolated, we have employed with success ethyl chloroformate and trifluoroacetic anhydride in mixed anhydride couplings. In one case where the acid chloride was extremely unstable (β-keto acid) we found that DCC works satisfactorily.

A simple example of doubly protected porphyrin can be constructed by treating the *trans*-**1a** with an excess of *p-tert*-butylbenzoyl chloride. The resultant *trans*-bis(*p-tert*-butylbenzamido)-DPE (**5**), isolated in >90% yield, possesses two phenyl rings held above and below the porphyrin ring. The protons of these phenyl groups were shifted upfield, δ 6.42 ($CDCl_3$), and appeared as a singlet in the NMR spectrum in a variety of solvents. The more crowded cis isomer, formed by the same sequence, showed the expected AB quartet for the benzamido phenyl protons in $CDCl_3$, but a singlet in Me_2SO-d_6. This result implies that the free rotation necessary to equilibrate the protons is restricted by solvation or aggregation in the cis, but not in the trans, atropisomer.

In order to prepare a series of pentacoordinate ferrous hemes needed in oxygen binding and other related studies, a stepwise coupling strategy was employed (Scheme II). Reaction of porphyrin **1a** with 1 equiv of *p-tert*-butylbenzoyl chloride followed by separation on silica gel yielded an almost statistical distribution of mono-, di-, and unsubstituted amino porphyrins. The monosubstituted porphyrin **6** can be easily appended with appropriate imidazole ligands. The imidazolyl alkanoic acids were synthesized by procedures analogous to those used in the synthesis of "tailed picket fence" porphyrin.[3b] However, there is evidence indicating that imidazoles appended via a straight chain alkyl linkage are somewhat undisciplined and tend to form mixtures of ligated and unligated ferrous hemes under many circumstances.[3b] A more orientation-specific imidazole ligand was designed by using the rigid benzamide linkage which also serves effectively as a blocking group, preventing the μ-oxo dimer formation in the ferric hemins. The synthesis was accomplished by coupling *m*-bromomethylbenzoyl chloride with the anilino porphyrin, followed by substitution with sodium imidazolate in acetonitrile. This two-step sequence overcame the low-solubility problem of *m*-[α-(*N*-imidazoyl)]toluic acid, but the benzyl halides formed were prone to hydrolysis during workup in the presence of organic bases. Hydrolysis could be prevented by simply reacting the benzyl halides in situ.

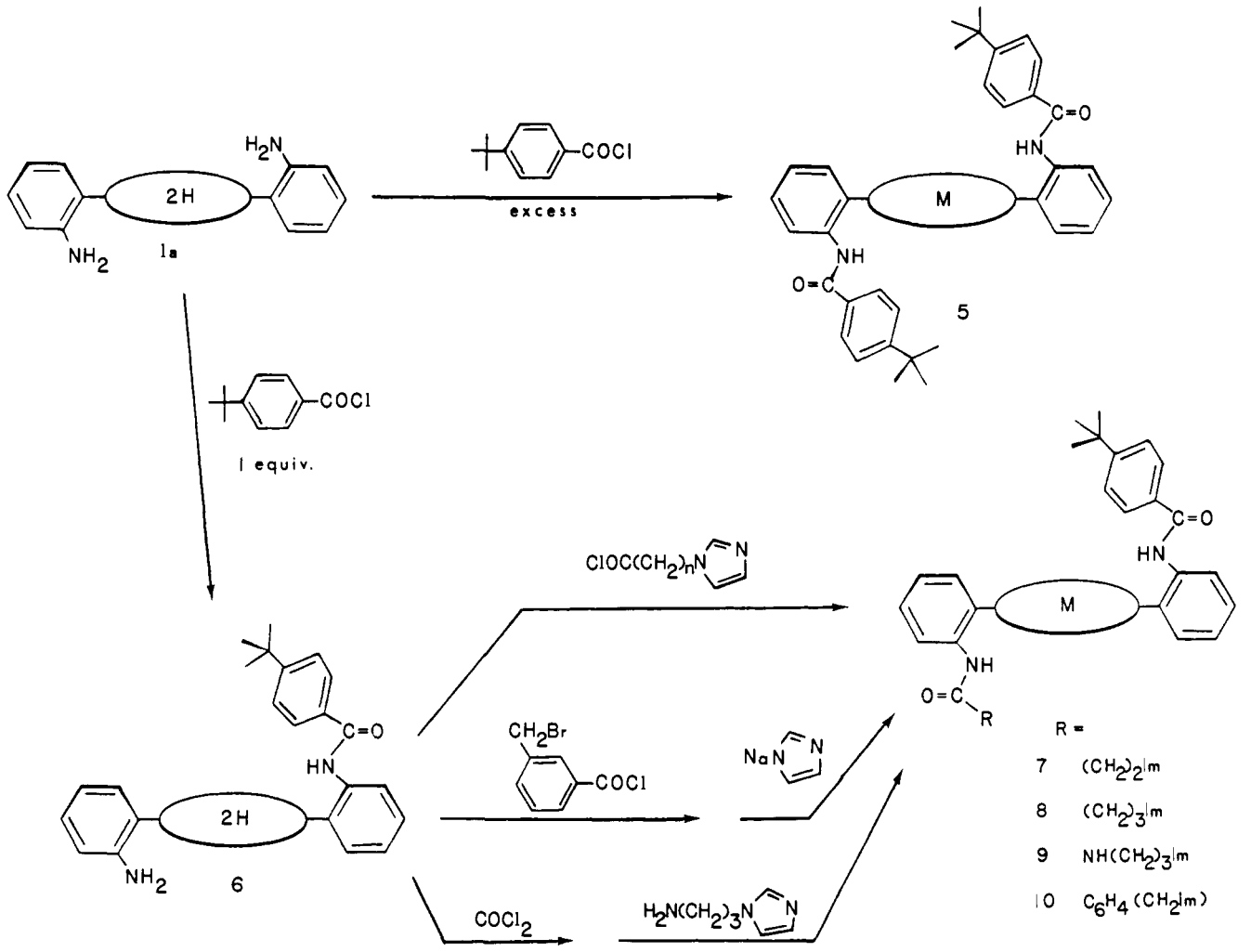
Modifications of the blocking group near the ligand coordination site (trans to the imidazole) were made in order to model the polarity and steric effects inside the myoglobin heme pocket. The monobenzylimidazole porphyrin **11** was easily prepared by treatment of the diamino DPE with 1 equiv of α-bromotoluic chloride, followed by addition of sodium imidazolate in acetonitrile, and subsequent separation of the product mixture. The monoimidazole porphyrin **11** can be carried through a variety of reaction sequences to produce blocked or functionally derivatized porphyrins of varying polarity and steric bulk (Scheme III). Although the iron complexes of most of these compounds did not form isolable oxygen adducts at room temperature, kinetic studies have shown that local polar groups assume a principal role in determining CO and O_2 binding.[7]

To prepare porphyrins **13–19**, large excesses of reagents were required to prevent cross-coupling and polymerization. Two methods were generally employed for crude purification before final separation on preparative TLC plates or columns, both utilizing the difference in basicity between the desired porphyrin and byproducts. The first method involved extraction of the porphyrins into 80% phosphoric acid, several washings with methylene chloride, and subsequent neutralization and extraction. The second method, generally giving a higher recovery, involved chromatographic separation of the protonated species. Reaction mixtures were protonated with acetic acid and then washed through a column of silica gel. The byproducts were eluted with methylene chloride–acetic acid, followed by the desired porphyrin which was freed with triethylamine.

Thermal Atropisomerization. The isolation of atropisomers in tetraphenylporphyrins and now diphenylporphyrins is evidence for the restricted rotation of phenyl rings. To allow ring rotation, the porphyrin skeleton must undergo severe deformations to minimize steric constraints between ortho substituents and pyrrole protons or ring methyl groups. The energy barrier for this rotation by thermal and photochemical processes in TPP derivatives has been the subject of an investigation.[8]

(8) Freitag, R. A.; Mercer-Smith, J. A.; Whitten, D. G. *J. Am. Chem. Soc.* **1981**, *103*, 1226.

Scheme II



The activation energies for thermal rotation in the *o*-diamino and *o*-diacetamido-DPE have been obtained. The kinetic studies were carried out by monitoring the rate of isomerization using thin-layer chromatography and UV–vis spectroscopy at several different temperatures. Table I lists the temperatures, rates, and $\Delta G^{\ddagger}$ calculated for the acetamido, amino, and related TPP systems.

The slower rates for the diamino vs. diacetamido-DPE are expected because of the size of substituent. The value of 28 kcal/mol of diacetamido is comparable to those of acyl derivatized tetra(*o*-aminophenyl)porphyrins.[8] Intuitively, the addition of flanking methyl groups should bring more hindrance than the β-pyrrole protons in preventing rotation. However, the absence of an increase in $\Delta G^{\ddagger}$ for the DPE system suggests that this is not true. This may be due to the more flexible nature of the diphenyl porphyrin. To minimize interaction between phenyl rings and β-substituents during rotation, the ring skeleton must twist around the methine carbons. In comparison with TPP, two phenyl rings are replaced by two protons at the meso positions, ring distortions may occur easier in the DPE systems. Therefore the added steric constraints introduced by the β-methyl groups may be compensated by the greater flexibility of diphenylporphyrin.

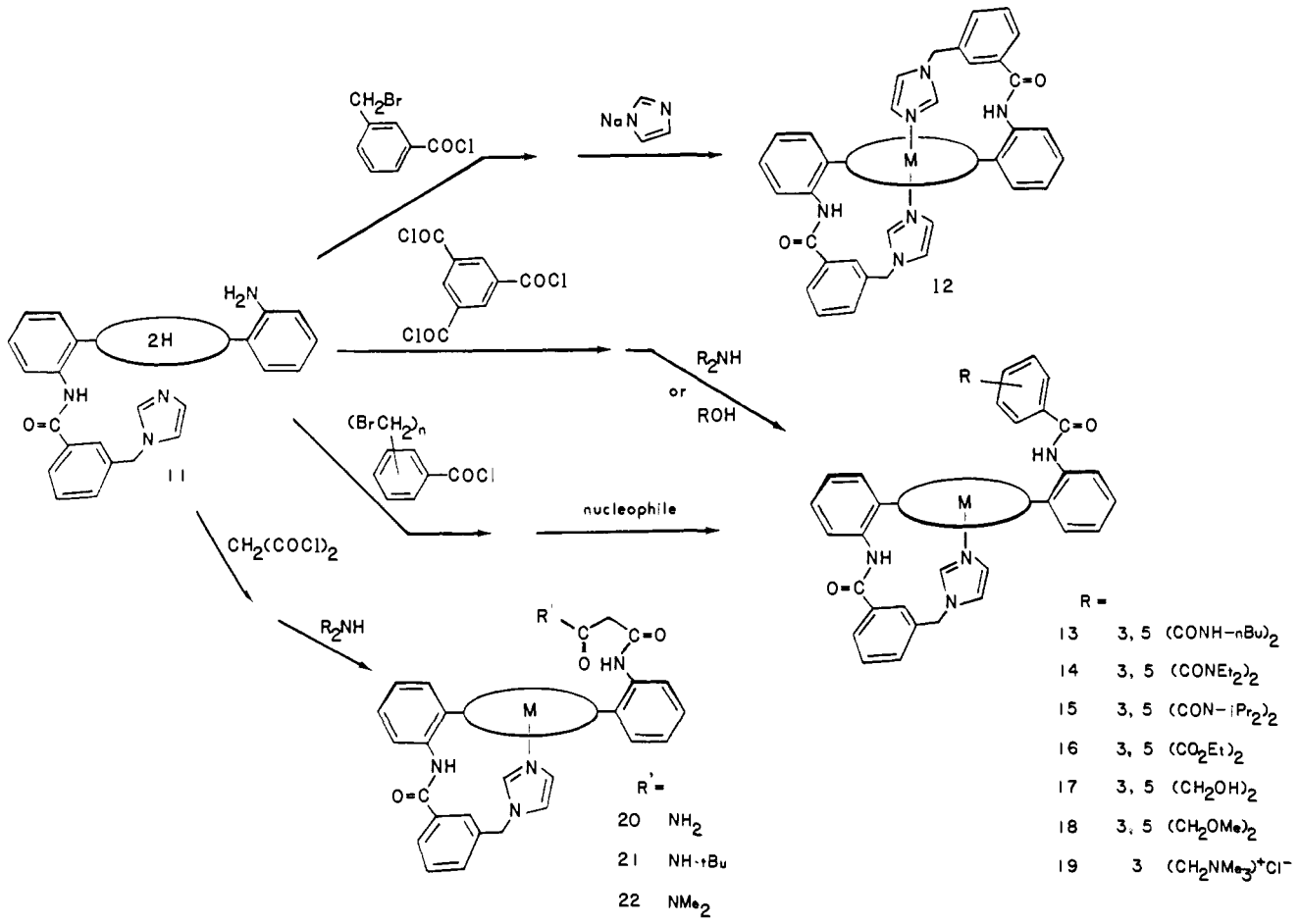
^{1}H NMR of Free Base Porphyrins. The ^{1}H NMR spectra of all free-base porphyrins recorded on a 250-MHz instrument have proven essential in the identification of mono- and disubstituted porphyrins used in construction of these unique heme models. As shown in Figure 1, the ring methyl groups flanking the phenyl rings in the DPE derivatives appear uniformly shifted ca. 1 ppm upfield vs. etioporphyrin II due to the diamagnetic ring current of phenyl rings. The peripheral ethyl groups and methine protons are not affected by the phenyl rings but would be expected to reflect any reduction in porphyrin ring current if large distortions in the skeleton are present. Since no deviation was observed, we believe that the DPE derivatives are essentially as flat as other ordinary porphyrins. The ring methyl groups serve as a diagnostic tool in probing the symmetry of products. Parts A, C, and D of Figure 1 illustrate unsubstituted and symmetrically substituted systems, showing only a singlet for the ring methyls. Parts B and E of Figure 1 are typical of asymmetric substitutions, hence a pair of singlets for the four methyl groups. The ethyl groups also reflect symmetry but patterns are more complex. In the aromatic region, amide formation causes large downfield shifts of the protons ortho to the amine, due to deshielding by the carbonyl group. The N–H

Table I. Rate Constants and Activation Energies for the Thermal Atropisomerization of Meso-Substituted Phenylporphyrins[a]

diphenylporphyrin	T, °C	k, s^{-1}	$\Delta G^{\ddagger}$, kcal/mol
(acetamide)$_2$, cis	115	9.7×10^{-4}	28.2
	120	1.9×10^{-3}	28.0
	132	5.5×10^{-3}	28.1
	141	1.5×10^{-2}	27.9
(amino)$_2$, cis	87	7.9×10^{-4}	26.2
	98	2.6×10^{-3}	26.2
	109	7.8×10^{-3}	26.2
	112	1.1×10^{-2}	26.1
	123	2.5×10^{-2}	26.2
tetraphenylporphyrin	**T, °C**	**k, s^{-1}**	**$\Delta G^{\ddagger}$, kcal/mol**
(*o*-hexadecylamide)$_4$[b]	81	1.7×10^{-4}	27.0
	108	4.5×10^{-4}	28.3
	136	2.2×10^{-3}	29.2
(*o*-pivalylamide)$_4$[b]	108	2.5×10^{-5}	30.5
	138	5.6×10^{-4}	30.4

[a] In *o*-xylene. [b] Reference 8.

Scheme III



proton of the amide appears at δ 6.9 for aliphatic acids and δ 8 for benzoic acids, again due to deshielding by the phenyl ring held above.

The aromatic protons of the bis(*p-tert*-butylbenzamide) (Figure 1C,D) appear as singlets in the trans isomer but the expected AA'BB' pattern in the cis isomer. In Me_2SO-d_6, both compounds exhibit singlets for these protons. The cis isomer is more congested than the trans isomer and aggregation or solvation serves to prevent free rotation and equilibration of the aromatic protons.

Sterically Protected Heme and Hemin Hydroxide. It is well-known that in the presence of OH^-, ferric hemes dimerize in solution to yield the Fe–O–Fe μ-oxo species, which makes the isolation of hemin hydroxide nearly impossible for most iron porphyrins.[9] The μ-oxo dimer is also formed when ferrous hemes undergo autoxidation.[10] This is the major drawback in the use of simple heme as a model for studying O_2 binding in hemoglobin and myoglobin. In the protein, the heme prosthetic group is invariably immobilized within the polypeptide matrix; therefore, formation of hemin hydroxide (hematin) is commonplace. In fact, such hydroxide species may be crucial in the enzymatic functions of catalase, peroxidase, and cytochrome oxidase.

In order to prevent μ-oxo dimer formation in iron porphyrins, steric blockage must be incorporated to protect both faces of the heme group. A large number of encumbered heme models aiming at producing stable O_2 complexes have been synthesized,[1-3] but these compounds are generally protected only on one side. Only recently have studies been made on the preparation of doubly protected system capable of forming hemin hydroxide. The formation of hemin hydroxides has been observed with meso-substituted (5-anthryl)porphyrins.[11,12] Balch and co-workers synthesized ferric hydroxides of tetra(2,4,6-trimethoxyphenyl)-porphyrin and tetramesitylporphyrin via air oxidation of ferrous hemes or by metathesis of hemin chloride with aqueous sodium hydroxide.[13] Hemin hydroxide of a "bis-pocket" tetrakis(2,4,6-triphenylphenyl)porphyrin was also prepared by Suslick.[14] Except for Balch's work, most of these compounds are difficult to make and have not been fully characterized. Our *trans*-amino-DPE, if properly derivatized, should offer a simple alternative for the preparation of hemin hydroxide.

Both the *cis*- and *trans*-bis(*p-tert*-butylbenzamido)-DPE (**4** and **5**) were converted to the hemin chloride by standard procedures. Exchange of the anion was carried out either by elution of the halide through basic alumina or washing a dichloromethane solution with aqueous NaOH. After completion of the exchange, as evidenced by changes in the visible spectra (Figure 2), the solutions were dried and evaporated to dryness. The cis isomer dimerized readily to the thermodynamically more stable μ-oxo dimer as shown by spectral changes, and can be easily crystallized from methanol–CH_2Cl_2. The trans hemin hydroxide did not dimerize upon isolation but crystallization in methanol often gave mixtures due to the formation of methoxide. Thus, a solid form of hemin hydroxide was obtained by lyophilization from benzene or precipitation from hexane.

Cyclic voltammograms of the cis and trans hemin chlorides, as expected, are identical. However, the isolated products following metathesis are unique. As shown in Figure 3, the voltammogram of the open-face cis isomer is indicative of a μ-oxo dimer exhibiting oxidation of both rings in a stepwise fashion. The voltammogram of the trans product indicates that $E_{1/2}$ for the Fe(III)/Fe(II) couple is about 500 mV more negative in the hydroxide than in the chloride. The greater difficulty in reduction can be accounted

(9) Cohen, I. A.; Caughey, W. S. *Biochemistry* **1968**, *7*, 636.
(10) Ching, D. H.; La Mar, G. N.; Balch, A. L. *J. Am. Chem. Soc.* **1980**, *102*, 4344.
(11) Cense, J. M.; Le Quan, R.-M. *Tetrahedron Lett.* **1979**, 3725.
(12) Harel, Y.; Felton, R. H. *J. Chem. Soc., Chem. Commun.* **1984**, 206.
(13) Cheng, R.-J.; Latos-Grazynski, L.; Balch, A. L. *Inorg. Chem.* **1982**, *21*, 2412.
(14) Suslick, K. S.; Fox, M. M. *J. Am. Chem. Soc.* **1983**, *105*, 3507.

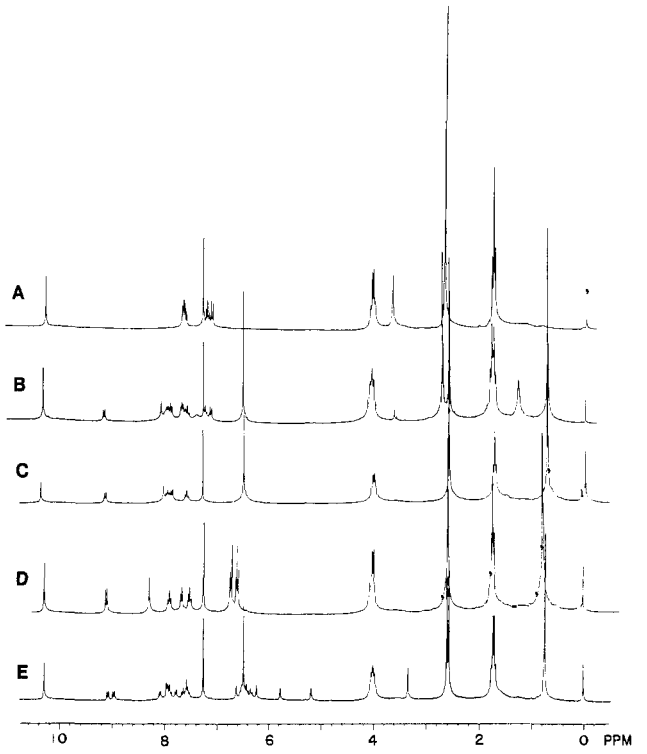


Figure 1. ^{1}H NMR spectra of free base diphenylporphyrins (in $CDCl_3$): *trans*-diamino-DPE (**1a**) (A); *trans*-monoaminomono(*tert*-butylbenzamido)-DPE (**6**) (B); *trans*-bis(*tert*-butylbenzamido)-DPE (**5**) (C); *cis*-bis(*tert*-butylbenzamido)-DPE (**4**) (D); *trans*-mono(*tert*-butylbenzamido)mono(*N*-imidazolyl)toluamido-DPE (**10**) (E).

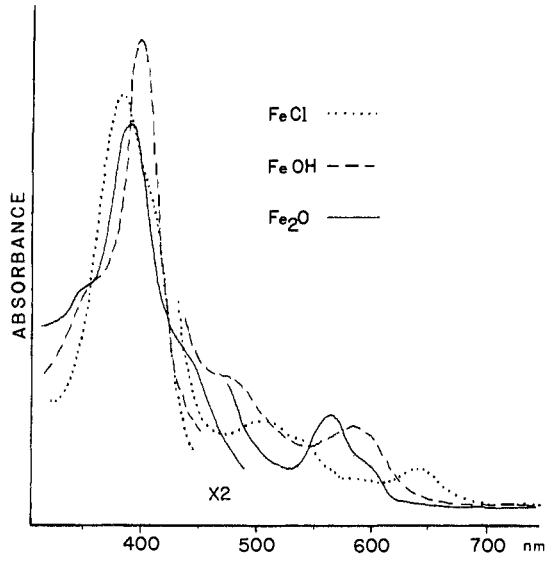


Figure 2. UV–vis absorption spectra of Fe(III) complexes of bis(*tert*-butylbenzamido)-DPE **4** or **5**, in CH_2Cl_2: *cis*-FeCl (···); *trans*-FeOH (---); and *cis*-μ-oxo dimer (—).

for by the higher electron density of the central metal, due to the electron donating ability of the hydroxide ligand.

Infrared spectroscopy provided unambiguous evidence of the presence of an OH group in the trans product. The hydroxide exhibits a sharp peak at 3615 cm^{-1}, which is absent in either the trans chloride or the cis μ-oxo dimer. Previous workers have sometimes used this peak as the sole evidence for the presence of hemin hydroxide.[12,15,16] Balch and co-workers,[13] however, did not observe this peak in any of their systems, only a broad band centered at 3400 cm^{-1} which can be attributed to occluded water.

The ^{1}H NMR of the cis μ-oxo dimer, Figure 4, is indicative of a strongly coupled species; there are no resonances beyond δ

(15) Botulinski, A.; Buchler, J. W.; Ensling, J.; Twilfer, H.; Billecke, J.; Leuken, H.; Tonn, B. *Adv. Chem. Ser.* **1982**, *No. 201*, 253.
(16) Gunter, M. J.; Mander, L. N.; Murray, K. S. *J. Chem. Soc., Chem. Commun.* **1981**, 799.

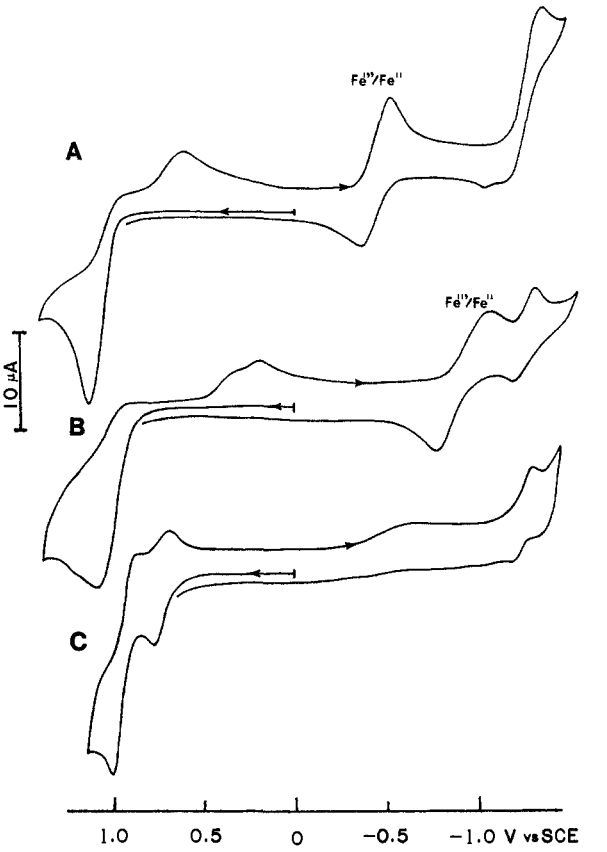


Figure 3. Cyclic voltammograms of Fe(III) complexes of bis(*tert*-butylbenzamido)-DPE (**4** or **5**): *trans*-FeCl (A); *trans*-FeOH (B); *cis*-Fe–O–Fe (C), in CH_2Cl_2 containing 0.1 M tetrabutylammonium perchlorate, under argon.

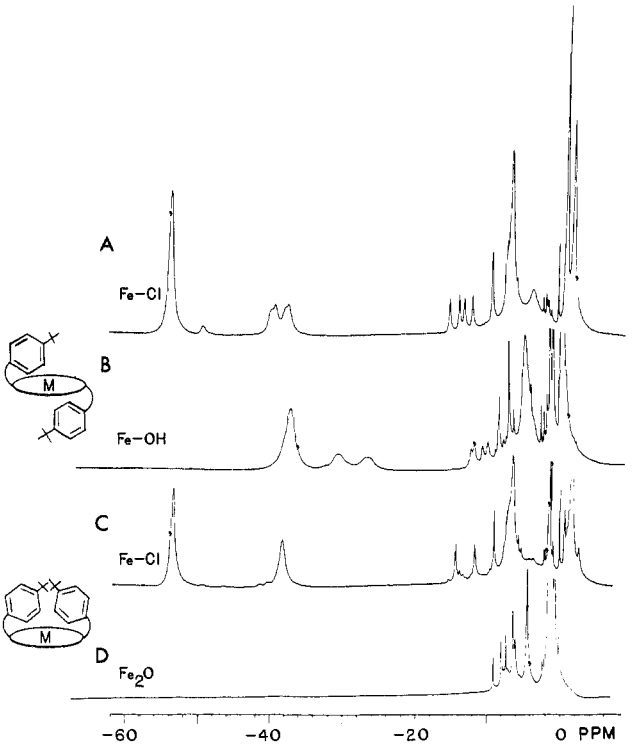


Figure 4. ^{1}H NMR spectra of bis(*tert*-butylbenzamido)-DPE complexes: *trans*-FeCl (A); *trans*-FeOH (B); *cis*-FeCl (C); *cis*-Fe-O-Fe (D), in $CDCl_3$.

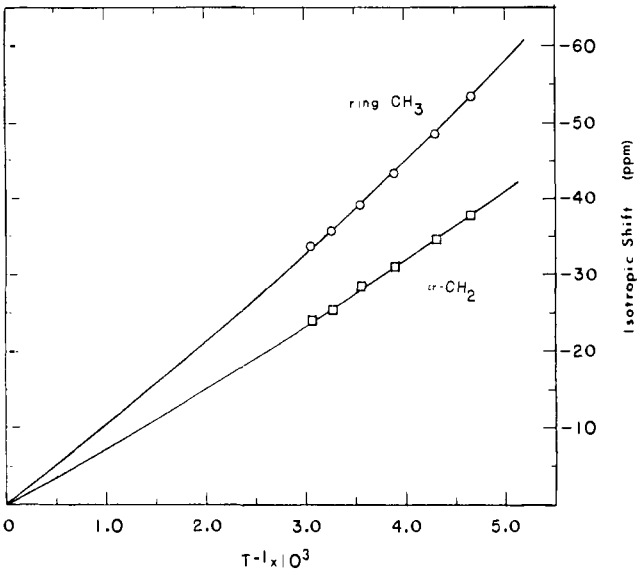


Figure 5. Curie plots for the proton resonances of *trans*-bis(*tert*-butylbenzamido)-DPE (**5**) $Fe^{III}OH$ in $CDCl_3$).

-10. (For paramagnetic species, we conform to the convention that downfield shifts from Me_4Si take the negative sign.) The trans hydroxide shows large isotropic shifts for the ring methyl groups and the CH_2 protons centered at δ -38 and -30, respectively. The features of this spectrum are similar to the high-spin ferric hemin chloride: there are large isotropic shifts and splitting of CH_2 and *tert*-butyl peaks. The isotropic shifts of the trans hydroxide also exhibit a near Curie behavior with a linear dependence on reciprocal of temperature (Figure 5). The curvature of the Curie plot can be accounted for by the dipolar contribution[17] to the isotropic shift

$$H/H_0 = C_{con}/T + C_{dip}/T^2$$

where

$$C_{con} = -A/h[35g\beta/(12k\gamma_H/2\pi)]$$

$$C_{dip} = 28g^2\beta^2(3\cos^2\theta - 1)D/9k^2r^3$$

The calculated value of D is 10.0 cm^{-1}, very similar to that measured for the tetramesitylporphyrin Fe–OH.[13]

The observed change in the isotropic shifts between hemin chloride and hydroxide for our *trans*-bis(*p-tert*-butylbenzamido)-DPE is 15 ppm, which is quite large in comparison with the ca. 1 ppm difference observed for the tetramesitylporphyrin system. In principle, isotropic shifts are extremely sensitive to spin-density variations caused by ligand or conformational changes. Large changes in isotropic shifts have been observed in ferric hydroxide of porphodimethenes.[15] The sensitivity of the shifts of α-CH_2 units in 5,15-dimethyloctaethylporphodimethene were attributed to the folding of the ring skeleton, resulting in reduced transfer of spin density from the metal to the ring. The flexibility of the diphenyl porphyrin system has already been alluded by the ease of atropisomerization. It is possible that the large changes in isotropic shift may be related to the intrinsic flexibility of the DPE ring. Whether or not the DPE hemin hydroxide exists with a folded ring structure is an interesting question which can be illuminated by X-ray crystallography.

Hemes Appended with Imidazole Ligands. The importance of the proximal histidyl imidazole in hemoglobin and myoglobin oxygen binding has been well established. The histidyl ligand is also present in other heme proteins such as cytochromes *c*, b_5, cytochrome oxidase, and peroxidases. Therefore, it is not surprising that imidazole–iron porphyrin complexes have been and continue to be a crucial model in biomimetic studies of heme-containing systems. However, the use of free imidazoles and simple hemes to generate 5-coordinate complexes is not possible due to the competing reaction to form 6-coordinate hemochromes. In compounds that are sterically protected on one face of the porphyrin ring, i.e., capped, crowned hemes,[1,2] and cofacial diporphyrins,[2f,18] a bulky imidazole can be used effectively to prevent bis coordination. In other less shielded systems, including our *p-tert*-butylbe ızamide-DPE derivatives, this approach is unsatisfactory. An alternative to generating 5-coordinate heme without the use of external ligand is to covalently attach an imidazole to the heme group. This tactic originally reported by Warme and Hager[19] and later successfully employed by Chang and Traylor[20] to allow equilibrium and kinetic studies of O_2 binding to a variety of myoglobin models has attracted continued exploitations in more recent heme model studies.[21] The main advantage of strapped bases is the generation of a high local concentration of ligand near the metal center. In addition, perturbations affecting the imidazole coordination can be easily introduced by modifying the side chain or spacer group connecting the base and the ring. This arrangement also more closely resembles the natural system where the interaction between heme iron and histidine is subject to protein conformational controls. Indeed, studies by Traylor and coworkers have shown that strain introduced by chain length or substitution has a dramatic effect on the electronic, spectroscopic, and chemical properties of heme models.[22]

Alkyl-chain-linked imidazoles can be easily added to the DPE system by using two routes (Scheme II). The *trans*-mono-*tert*-butylbenzamidomonoamino-DPE **6** was coupled with *N*-imidazolylalkanoic acid chlorides of varying length. Alternatively, porphyrin **6** was reacted with phosgene to generate the carbamoyl chloride which when combined with ω-amino appendages produced the urea-linked system in excellent yields. The structures of these imidazole-appended DPE's were characterized by NMR, IR, and elemental analyses. ^1H NMR spectra of the diamagnetic zinc complexes of these compounds provided additional support for the purported structure. Zinc porphyrins, prepared by heating the porphyrin with a saturated methanolic solution of zinc acetate in methylene chloride, bind imidazole strongly. Thus, coordination of the intramolecularly linked base resulted in the disappearance of imidazole protons and the upfield shift of the alkyl-strap protons which are held rigidly over the ring. Conversely, the addition of trifluoroacetic acid resulted in protonation of imidazole and disruption of coordination, thereby causing downfield shift for the methylene protons as the side chain moved away from the porphyrin.

Our previous experience as well as the experiments described below suggest that an alkyl chain strapped imidazole is still able to form both inter- and intramolecular complexes. In an effort to construct a more restricted system, porphyrin **12** (also **10** and **13–22**) was designed (Scheme III). The *m*-benzyl linkage is less floppy and has fewer degrees of rotation freedom than alkyl straps. Synthetically, the imidazolyl *m*-toluic acid chloride was difficult to obtain because of the insolubility of the acid. A two-step method was therefore devised as described in the Synthesis section. The advantage of the benzyl linked imidazole is illustrated by the following ^1H NMR experiments using ferric hemes.

At room temperature, mixing a 2:1 stoichiometric ratio of 1-methylimidazole and the *trans*-diacetamido-DPE-$Fe^{III}Cl$ gave a spectrum (Figure 6) typical of high-spin ($s = {}^5/_2$, d^5) species, which shows that 2 equiv of external base is not sufficient to form appreciable amounts of 6-coordinate hemichrome. The equilibrium, of course, can be shifted to the bis(imidazole) complex by addition of excess base or lowering the temperature. As tem-

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(21) (a) Traylor, T. G.; Stynes, D. V. *J. Am. Chem. Soc.* **1980**, *102*, 5938. (b) Traylor, T. G.; Campbell, D.; Sharma, V.; Geibel, J. *J. Am. Chem. Soc.* **1979**, *101*, 5376.
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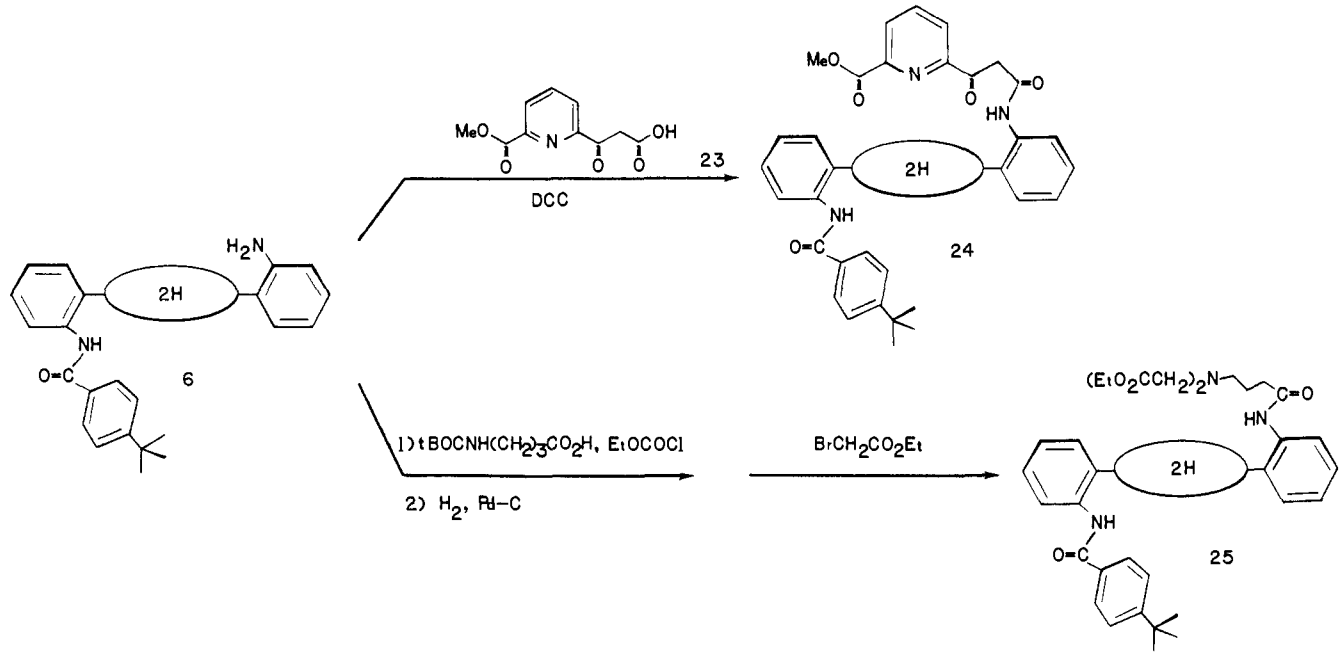
Scheme IV



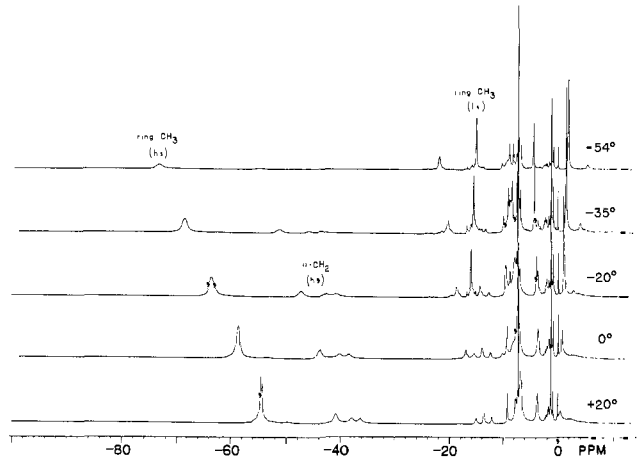


Figure 6. Temperature-dependent ^1H NMR spectra of $CDCl_3$ solution containing 0.01 M bis(acetamido)-DPE $Fe^{III}Cl$ and 0.02 M *N*-methylimidazole.

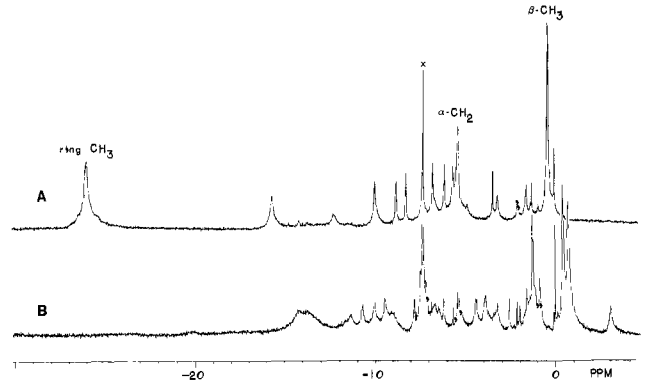


Figure 7. Comparison of ^1H NMR of intramolecularly bound bis(imidazole) complexes of diphenyl hemins: *trans*-bis(*N*-imidazolyl)toluamido-DPE (**12**) (A); *trans*-bis(*N*-imidazolyl)propylureido-DPE (**9**) (B), in $CDCl_3$.

perature was reduced, the spin equilibrium became obvious. Complete conversion to the 6-coordinate low-spin complex, however, was prevented by solubility limitations. The higher local concentration of imidazole in strapped imidazoles is seen in the spectrum of the bis(urea-linked imidazole) heme (Figure 7B). At room temperature, only the low-spin species was observed. However, the appearance of ring methyl groups as broad bands as well as the splitting of the α-CH_2 protons when temperature was lowered suggests that mixtures of intra- and intermolecularly bound species exist in solution.

The bis(benzylimidazole) heme exhibited a relatively sharp resonance at δ −26 corresponding to the ring methyl protons (Figure 7A). Also as the temperature was reduced, the ring methyl and α-CH_2 resonances remained as sharp singlets, reflecting a high degree of symmetry in the bis(imidazole) complex. There was no indication of exchange.

The large downfield shift of the ring methyl groups, observed at δ −26 in the bis(benzylimidazole) system is noteworthy. The ring methyl resonances of bis(imidazole) complexes of other porphyrins usually occur around δ −15.[23] As well, extrapolation of the shifts for noncovalently linked *N*-methylimidazole–diphenylheme system gives a signal around δ −17 at room temperature; for free *N*-benzylimidazole plus diacetyl-DPE hemin chloride, the peak is estimated at δ −16. To determine the influence of the appended benzylimidazole, a mixed species consisting of *trans*-mono(*tert*-butylbenzamido)monoimidazolyltoluamido-DPE-$Fe^{III}Cl$ (**9**) and imidazole was prepared. The presence of the appended benzylimidazole to create a high local concentration facilitated coordination of the second (free) imidazole to form a bis adduct with only a small excess of imidazole. The ring methyl protons appeared as a doublet in this system, indicating asymmetric coordination. Interestingly, the shift was normal: −15.1 and −15.3 ppm.

These results concur with the previous observation that the spin-density distribution at the peripheral substituents of ferric heme is very sensitive to axial ligand orientation or ring distortion.[24-26] The covalently bound bis(benzylimidazole) either introduced distortion to the ring or, more likely, assumed a coordination geometry at variance with the free ligand. In the mixed complex, the shift is normal because whatever distortion brought about by the internal ligand is compensated by the external ligand.

(23) For example: etioporphyrin I bis(imidazole) hemichrome: δ −15.

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(25) Goff, H. *J. Am. Chem. Soc.* **1980**, *102*, 3252.
(26) (a) Walker, F. A. *J. Am. Chem. Soc.* **1980**, *102*, 2844. (b) Walker, F. A.; Buchler, J.; West, J. T.; Hinds, J. L. *J. Am. Chem. Soc.* **1983**, *105*, 6923.

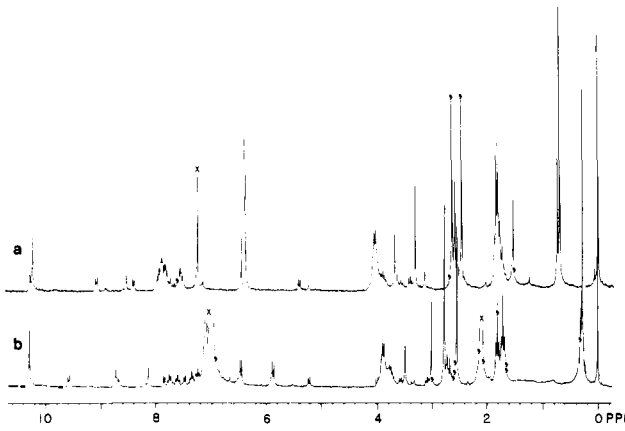

Figure 8. ^{1}H NMR spectra of the pyridyl keto DPE **24** in $CDCl_3$ (A) and in toluene-d_8 (B).

β-Ketoamide Appendages. In our effort to construct orientation specific groups appended to hemes, we also explored the use of β-ketoamido groups as linking unit. β-Carbonyl groups may form hydrogen bond to the amide bond, thereby, directing the attached functional groups over the porphyrin ring. Several routes leading to this type of compounds have been pursued. The malonyl amide porphyrins **20–22** were synthesized by first reacting the mono-imidazolyltoluamido-DPE (**11**) and an excess of malonyl dichloride, followed by treating the mixture with the amine to be attached. A pyridine ligand was also incorporated to a DPE according to Scheme IV. The mono ester of dipicolinic acid[27] was converted to the β-keto acid using lithio bis(trimethylsilyl) malonate.[28] The unstable β-ketopyridine acid **23** was successfully coupled to the *trans*-mono-*tert*-butylbenzamido-DPE **6** with DCC in methylene chloride with an almost quantitative yield. The effectiveness of DCC in this synthesis is remarkable since we have found little success in the use of this reagent in coupling other acids with tetra(*o*-aminophenyl)porphyrins, possibly due to steric congestions. The condensation of DPE with the pyridine keto acid also proceeded well using diimidazole carbonyl, albeit at a much retarded rate.

The ability of the β-ketoamide linkage in directing groups over the porphyrin is indicated by ^{1}H NMR spectra of the malonyl derivatives. These compounds clearly display an upfield shift for the terminal *N*-alkyl groups. For example, the *tert*-butyl protons appear as a singlet at δ 1.3 in *tert*-butylacetamide, but at δ 0.6 in the malonyl porphyrin. Similar behavior is observed for the *N,N*-dimethyl system, indicating that the terminal alkyl group is indeed hung over the porphyrin ring.

An interesting phenomenon was observed with the β-keto pyridine porphyrin **24**. Analysis of the ^{1}H NMR spectrum in $CDCl_3$ (Figure 8) revealed the presence of two species, one symmetric and one asymmetric in a ratio of 3:2, respectively. Evidence for the symmetry of the two products is indicated by the ring methyl protons which appeared as one intense singlet and a pair of two smaller, equal intensity singlets. In different solvent, the ratio of these peaks varied. For example, in toluene-d_8, only the unsymmetric species was detected. The asymmetry which may arise from enolization of the β-keto amide, is seen as splittings of the ring methyl protons and dissimilarity of the aromatic protons ortho to the amide.

Kinetic studies of CO binding to the malonamide appended hemes have been carried out for the purpose of determining any distal steric effects brought about by these peptide-like blocking groups. However, little differences were found in the CO association rate as the amide varied from primary, secondary, to tertiary.[29] Previously, it has been established that the CO association rate is sensitive to the steric crowdedness at the heme iron.[30,31] The lack of change in this rate would reflect the facts that the *N,N*-dialkyl substituents need not to be coplanar with the carbonyl group and that they can assume conformations which have a minimum interaction with the incoming ligand. Thus, it may be difficult to control or predict the distal steric effect of the malonamide appendages.

The β-keto pyridine ligand was designed with the goal that binucleating porphyrins can be prepared. For that purpose, a related "half EDTA" appended porphyrin **25** was also synthesized (Scheme IV). The stepwise approach via a protected aminobutyric acid was necessary since attempts to construct the ligand prior to coupling failed. ^{1}H NMR of the free base porphyrin again showed distinctive shifts of the CH_2 protons due to the ring current effect. Several dimetal systems such as Cu–Cu and heme–Cu complexes have been successfully prepared for saponified **24** and **25**. Their spectroscopic and magnetic properties will be the subject of a separate publication.

Experimental Section

^{1}H NMR spectra were recorded on a Bruker WM-250 MHz instrument. Absorption spectra were measured by using a Cary 219 spectrophotometer. IR spectra were obtained in KBr wafers on a Perkin Elmer 237B spectrometer. Elemental analyses were performed by Spang; C, H, N analyses were within ±0.42%. Methylene chloride was distilled from CaH_2 and THF was distilled from $LiAlH_4$ before use.

Thermal Atropisomerization. To *o*-xylene (50 mL) heated to constant temperatures in an oil bath was added the *cis*-DPE (20 mg) in methylene chloride (5 mL). Aliquots were analyzed at intervals by TLC (silica gel, methylene chloride/hexane). The separated isomers were placed in a cuvette and diluted to a constant volume with 10% $MeOH/CH_2Cl_2$, and the relative absorbance was determined at 403 nm. The rates of isomerization were determined by least-squares plots.

^{1}H NMR. Free base and iron porphyrin were measured in $CDCl_3$ (ca. 0.01 M) at 20 °C. $Fe^{III}P(Im)_2$ was prepared by addition of an excess amount of imidazole in $CDCl_3$. $Fe^{II}P(Im)CO$ was prepared by mixing a $CDCl_3$ solution of the iron porphyrin with aqueous sodium dithionite under CO atmosphere.

Fe Insertion. Porphyrin (20 mg) was dissolved in 1:1 THF/benzene (20 mL), containing collidine (2 drops) and $FeBr_2$ (40 mg). The solution was heated under argon for ca. 30 min and the solvent was removed in vacuo. The residue was redissolved in CH_2Cl_2, extracted with 10% HCl, washed with water, and eluted on alumina column. To obtain the ferric chloride form, the solution was washed with saturated NaCl in 0.1 N HCl. The hydroxide was obtained by washing a CH_2Cl_2 solution with 10% NaOH. Alternatively, the hemin chloride was eluted through a basic column of alumina until the absorption spectra indicated complete ligand exchange.

4,4′-Diethyl-3,3′-dimethyl-2,2′-dipyrrylmethane (2). 5,5′-Bis(ethoxycarbonyl)-4,4′-diethyl-3,3′-dimethyl-2,2′-dipyrrylmethane (120 g, 0.4 mol), which was obtained easily from ethyl 4-ethyl-3,5-dimethylpyrrole-2-carboxylate,[32] was dissolved in hot ethanol (95%, 400 mL). To this solution after it was heated to a gentle reflux with stirring, a solution of NaOH (50 g/100 mL water) was added carefully through the condenser. Refluxing was continued for 2 h, after which the condenser was removed and the solution volume was reduced by evaporation to $^1/_3$. The mixture was diluted with water (150 mL) and then brought to a vigorous refluxing for 6 h without interruption. At the end of this period, a layer of brown oil was separated. The mixture was allowed to cool to room temperature, and the solidified material was filtered off, washed with water until neutral, and dried (quantitative yield). The freshly prepared decarboxylated dipyrrylmethane has a light tan color and a characteristic charred bone smell; it slowly darkens in the air but can be stored indefinitely in a refrigerator. NMR ($CDCl_3$) δ 1.12 (t, 6 H, Et), 2.03 (s, 6 H, Me), 2.47 (q, 4 H, Et), 3.79 (s, 2 H, CH_2), 6.35 (m, 2 H, 5-H), 7.26 (br s, 2 H, NH); mp 49–50 °C; MS, *m/e* 230 (M^+). Occasionally, the decarboxylated product contained the disodium salt of **2** as a white powder (mp 172–173 °C; MS, *m/e* 274) which can be used for the

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(28) Barnick, J. W. F. K.; Van der Baan, J. L.; Bickelhaupt, F. *Synthesis* **1979**, 787.
(29) CO association rates for unsubstituted malonamide, 2.5×10^6 (M^{-1} s^{-1}); *N,N*-dimethylmalonamide, 2.4×10^6; *N-tert*-butylmalonamide, 2.2×10^6, in toluene, at 23 °C.
(30) (a) Ward, B.; Wang, C. B.; Chang, C. K. *J. Am. Chem. Soc.* **1981**, *103*, 5236. (b) Traylor, T. G.; Mitchell, M. J.; Tsuchiya, S.; Campbell, D. H.; Stynes, D. V.; Koga, N. *J. Am. Chem. Soc.* **1981**, *103*, 5234. (c) Collman, J. P.; Brauman, J. I.; Iverson, B. L.; Sessler, J. L.; Morris, R. M.; Gibson, Q. H. *J. Am. Chem. Soc.* **1983**, *105*, 3052.
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following condensation without isolation or purification.

5,15-Bis(*o*-nitrophenyl)-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin. 4,4′-Diethyl-3,3′-dimethyl-2,2′-dipyrrylmethane 2 (6 g, 26.1 mmol) and *o*-nitrobenzaldehyde (3.9 g, 26.1 mmol) were dissolved in methanol (300 mL). After the solution was deaerated by bubbling with argon for 10 min, *p*-toluenesulfonic acid (1.4 g, 7.4 mmol) was added. The mixture was stirred for 15 min and then allowed to stand in the dark at room temperature. The crude yellow porphyrinogen began precipitating within 1 h. After 6 h at room temperature, the solution was cooled and kept at 4 °C overnight. The solid was collected and washed with cold methanol.

The crude porphyrinogen **3** (2.5 g) was dissolved in THF (200 mL) and treated with a solution of *o*-chloranil (2.5 g) in THF (20 mL). The solution was stirred at room temperature for 30 min. The porphyrin which precipitated out during this period was too finely divided to be filtered. Thus, the solvent was evaporated and the protonated residue was redissolved in methylene chloride. A solution of methanol–triethylamine (4:1) was added to reprecipitate the porphyrin. The product was collected by filtration and was washed with cold methanol and THF (yield, 2.2 g); NMR ($CDCl_3$–TFA) δ −1.84 (br s, 4 H, NH), 1.37 (t, 12 H, Me), 2.29 (s, 12 H, Me), 3.74 (q, 8 H, CH_2), 8.13 (m, 4 H, Ar), 8.48 (m, 4 H, Ar), 10.22 (s, 2 H, meso); UV–vis (dichloromethane) λ_{max} (ϵ_{mM}) 629 nm (2.5), 578 (6.3), 545 (5.8), 509 (15.0), 408 (150).

5,15-Bis(*o*-aminophenyl)-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin (1). To a solution of the (nitrophenyl)porphyrin (4 g, 5.5 mmol) dissolved in 12 N HCl (180 mL) was added stannous chloride dihydrate (9.4 g, 41.3 mmol). The mixture was stirred at room temperature for 16 h. The solution was diluted with water (100 mL), neutralized with aqueous ammonia (75 mL), and extracted with methylene chloride (3 × 100 mL). The combined organic layers were washed with water, dried, and evaporated to dryness. The crude porphyrin was redissolved in a minimum amount of CH_2Cl_2, acidified with trifluoroacetic acid (1 mL), and irradiated under a sun lamp for 2 h to recovery any overreduced porphyrin. At the end of this treatment, the solution was diluted with CH_2Cl_2, washed with water and saturated $NaHCO_3$, and then evaporated to dryness. The crude product was purified on a silica column (6 × 30 cm) using 2% methanol–CH_2Cl_2. The trans isomer was eluted first, followed sluggishly by the cis isomer. Yields from a 2 g crude mixture: trans, 0.74 g (37%) and cis, 1.1 g (55%).

Cis isomer 1b: mp >380 °C; NMR ($CDCl_3$) δ −2.43 (br s, 2 H, pyr-NH), 1.79 (t, 12 H, Et), 2.70 (s, 12 H, Me), 3.63 (s, 4 H, NH_2), 4.04 (q, 8 H, Et), 7.1 (d, 2 H, Ar), 7.19 (t, 2 H, Ar), 7.60 (t, 2 H, Ar), 7.67 (d, 2 H, Ar), 10.25 (s, 2 H, meso).

Trans isomer 1a: mp >380 °C; NMR ($CDCl_3$) δ −2.44 (s, 2 H, pyr-NH), 1.79 (t, 12 H, Et), 2.70 (s, 12 H, Me), 3.67 (s, 4 H, NH_2), 4.05 (q, 8 H, Et), m.10 (d, 2 H, Ar), 7.17 (t, 2 H, Ar), 7.57–7.65 (m, 4 H, Ar), 10.23 (s, 2 H, meso).

***trans*-5,15-Bis[*o*-(*p*-*tert*-butylbenzamido)phenyl]-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin (5).** A mixture of *p*-*tert*-butylbenzoic acid (2 g, 11.2 mmol) and thionyl chloride (2 mL) in chloroform (20 mL) was refluxed under nitrogen for 3 h. The solution was evaporated to dryness to yield a yellow oil.

A portion of the crude acid chloride (89 mg, 0.45 mmol) was dissolved in methylene chloride (10 mL) and added dropwise to a solution of bis(amino)porphyrin **1a** (300 mg, 0.45 mmol) in CH_2Cl_2 (100 mL) containing triethylamine (1 mL, 7.17 mmol). After completion of the addition, the mixture was refluxed for 2 h under nitrogen before being poured into water (100 mL). The organic layer was separated and washed successively with 5% HCl (150 mL), H_2O (150 mL), saturated $NaHCO_3$ solution (150 mL), and H_2O (150 mL). After drying over sodium sulfate, the mixture was evaporated to dryness and separated on a series of preparative silica gel TLC plates (Analtech 1500 μm) using CH_2Cl_2.

The first band, containing *trans*-bis[*o*-(*p*-*tert*-butylbenzamido)-phenyl]porphyrin (**5**), was collected and crystallized from CH_2Cl_2–MeOH to yield purple crystals (80 mg, 18%); IR: ν_{CO} 1670 cm^{-1}; NMR ($CDCl_3$) δ −2.33 (br s, 2 H, pyr-NH), 0.73 (s, 18 H, *t*-Bu), 1.75 (t, 12 H, Et), 2.60 (s, 12 H, CH_3), 4.05 (q, 12 H, Et), 6.42 (s, 8 H, Ar), 7.55 (t, 2 H, Ar), 7.82–7.96 (m, 4 H, Ar), 7.99 (s, 2 H, NH), 9.10 (d, 2 H, Ar), 11.32 (s, 2 H, meso). Anal. Calcd for $C_{66}H_{72}N_4O_2$: C, 80.78; H, 7.40; N, 8.57. Found: C, 80.63; H, 7.31; N, 8.42.

The second band, which is the major one, corresponds to *trans*-5-(*o*-aminophenyl)-15-[*o*-(*p*-*tert*-butylbenzamido)phenyl]porphyrin (**6**), was also crystallized from CH_2Cl_2–MeOH (186 mg, 50%); NMR ($CDCl_3$) δ −2.40 (br s, 2 H, pyr-NH), 0.70 (s, 9 H, *t*-Bu), 1.72 (t, 6 H, Et), 1.76 (t, 6 H, Et), 2.57 (s, 6 H, CH_3), 2.70 (s, 6 H, CH_3), 3.68 (s, 2 H, NH_2), 4.05 (m, 8 H, Et), 6.47 (s, 4 H, Ar), 7.10 (d, 1 H, Ar), 7.17 (t, 2 H, Ar), 7.5–7.95 (m, 6 H, Ar), 8.05 (s, 1 H, NH), 9.10 (d, 2 H, Ar), 10.26 (s, 2 H, meso). Anal. Calcd for $C_{55}H_{60}N_6O$: C, 80.45; H, 7.36; N, 10.24. Found: C, 80.22; H, 7.27; N, 10.16.

The third band was the recovered starting material, *trans*-5,15-bis(*o*-aminophenyl)porphyrin (**1a**) (92 mg, 31%).

***trans*-5-[*o*-*p*-*tert*-Butylbenzamido)phenyl]-15-{*o*-[*m*-(α-*N*-imidazolyl)toluamido]phenyl}-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin (10).** *m*-Toluic acid (10 g, 73.5 mmol) dissolved in nitrobenzene (60 mL) was heated to 125 °C. The solution was illuminated with a sun lamp while bromine (11.74 g, 73.5 mmol) was added dropwise. After the addition was complete (ca. 2 h), the solution was stirred 6 h further at 125 °C. The solution was then cooled and poured into petroleum ether (100 mL). The solid was collected and recrystallized from $CHCl_3$, mp 145–146 °C. α-Bromo-*m*-toluic acid (1.5 g, 6.98 mmol) and an excess of thionyl chloride (2 mL, 27.4 mmol) in methylene chloride (20 mL) was refluxed under N_2. After the solution had cleared and evolution of gas ceased (ca. 30 min), the excess $SOCl_2$ and CH_2Cl_2 were removed in vacuo to yield the crude acid chloride as a yellow solid.

A mixture of porphyrin **6** (40 mg, 0.0486 mmol) and α-bromo-*m*-toluic acid chloride (45 mg, 0.193 mmol) in CH_2Cl_2 (60 mL) was refluxed under N_2 for 2 h. The volume of the mixture was reduced to about 20 mL and an excess of sodium imidazolate (90 mg, 1 mmol) in CH_3CN (20 mL) was added all at once. The mixture was heated to refluxing and the progress of reaction was monitored by TLC. After the reaction was complete, the solution was diluted with water. The organic layer was separated and successively extracted with 5% HCl (100 mL), H_2O (100 mL), saturated $NaHCO_3$ (100 mL), H_2O (100 mL), dried over Na_2SO_4, and evaporated to dryness. The product was purified through a silica gel pad (3 × 15 cm) eluted with 5% MeOH/CH_2Cl_2.

Recrystallization from hexane–CH_2Cl_2 yielded purple flakes, 41.5 mg (84%). NMR ($CDCl_3$) δ −2.31 (s, 2 H, pyr-NH), 0.73 (s, 9 H, *t*-Bu), 1.74 (m, 2 H, Et), 2.57 (s, 6 H, CH_3), 2.60 (s, 6 H, CH_3), 3.38 (s, 2 H, $ArCH_2$), 4.00 (m, 8 H, Et), 5.18 (s, 1 H, lm-H), 5.76 (s, 1 H, lm-H)), 6.22 (s, 1 H, Im-H), 6.25–6.6 (m, 8 H, Ar), 7.25–8.1 (m, 8 H, Ar NH), 8.96 (d, 1 H, Ar), 9.08 (d, 1 H, Ar), 10.29 (s, 2 H, meso). Anal. Calcd for $C_{66}H_{68}N_8O_2$: C, 78.85; H, 6.82; N, 11.15. Found: C, 78.59; H, 6.78; N, 10.96.

***trans*-5-(*o*-Aminophenyl)-15-{*o*-[*m*-(α-*N*-imidazolyl)toluamido]-phenyl}-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin (11).** α-Bromo-*m*-toluic acid chloride (70.8 mg, 0.304 mmol) was added to a methylene chloride (200 mL) solution of the diaminoporphyrin **1a** (200 mg, 304 mmol). The green solution was refluxed under N_2 for 3 h. The volume was reduced to $^1/_3$ and a solution of sodium imidazolate (500 mg, 55 mol) in acetonitrile (100 mL) is added. The mixture is refluxed for 2 h further before evaporated to dryness. The residue was redissolved in CH_2Cl_2 (150 mL), extracted successively with water (2 × 200 mL), 5% HCl (200 mL), H_2O (200 mL), saturated $NaHCO_3$ (200 mL), and H_2O (200 mL). After drying over Na_2SO_4, the organic layer was evaporated to dryness. The reaction mixture was separated on silica gel columns (4 × 30 cm). The least polar band corresponding to the starting material (64 mg, 32%) was eluted with 100% CH_2Cl_2. The second band which contains the desired porphyrin was eluted with 3% MeOH/CH_2Cl_2. The product was further crystallized from hexane–CH_2Cl_2 to give purple flakes (122 mg, 48%); NMR (CH_2Cl_2) δ −2.32 (br s, 2 H, pyr-NH), 1.72 (m, 12 H, Et), 2.60 (s, 6 H, CH_3), 2.70 (s, 6 H, CH_3), 3.22 (s, 2 H, $ArCH_2$), 3.68 (s, 2 H, NH_2), 4.02 (q, 8 H, Et), 5.18 (s, 1 H, lm-H), 5.64 (s, 1 H, lm-H), 6.25–6.63 (m, 5 H, Ar, lm-H), 7.10 (d, 1 H, Ar), 7.19 (t, 1 H, Ar), 7.5–7.7 (m, 4 H, Ar, NH), 7.93 (t, 1 H, Ar), 8.10 (d, 1 H, Ar), 8.96 (d, 1 H, Ar), 10.25 (s, 2 H, meso). Anal. Calcd for $C_{55}H_{68}N_8O$: C, 78.17; H, 6.68; N, 13.26. Found: C, 78.24; H, 6.80; N, 13.07.

***trans*-5,15-Bis{*o*-[*m*-(α-*N*-imidazolyl)toluamido]phenyl}-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin (12a).** In the above synthesis, the last band eluted with 10% MeOH/CH_2Cl_2 was the bis(imidazole)-porphyrin **12a**. It was recrystallized from hexane–CH_2Cl_2 to afford purple flakes (37 mg, 12%); NMR ($CDCl_3$) δ −2.32 (s, 2 H, pyr-NH), 1.73 (t, 12 H, Et), 2.58 (s, 12 H, CH_3), 3.33 (s, 4 H, $ArCH_2$), 4.00 (q, 8 H, Et), 5.16 (s, 2 H, Im-H), 5.78 (s, 2 H, lm-H), 6.19 (s, 2 H, lm-H), 6.30 (d, 2 H, Ar), 6.40 (t, 2 H, Ar), 6.52 (d, 2 H, Ar), 6.60 (s, 2 H, Ar), 7.57 (s, 2 H, NH), 7.64 (t, 2 H, Ar), 7.93 (t, 2 H, Ar), 8.05 (d, 2 H, Ar), 8.96 (d, 2 H, Ar), 9.29 (s, 2 H, meso). Anal. Calcd for $C_{66}H_{76}N_{10}O_2$: C, 76.12; H, 7.36; N, 13.45. Found: C, 76.05; H, 7.21; N, 13.47.

***cis*-5,15-Bis{*o*-[*m*-(α-*N*-imidazolyl)toluamido]phenyl}-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin (4).** This compound was resulted accompanying the preparation of the cis-monoimidazole porphyrin, analogous to the trans system; NMR ($CDCl_3$) δ −2.31 (br, s, pyr-NH), 1.71 (t, 12 H, Et) 2.57 (s, 12 H, CH_3), 3.53 (s, 4 H, $ArCH_2$), 3.97 (m, 8 H, Et), 5.08 (s, 2 H, lm-H), 5.50 (s, 2 H, lm-H), 5.84 (s, 2 H, lm-H), 5.92 (s, 2 H, Ar), 6.35 (d, 2 H, Ar), 6.45 (t, 2 H, Ar), 6.73 (d, 2 H, Ar), 7.62 (t, 2 H, Ar), 7.92 (t, 2 H, Ar), 8.09 (d, 2 H, Ar), 8.32 (s, 2 H, NH), 8.90 (d, 2 H, Ar), 9.03 (s, 2 H, meso).

***trans*-5-{*o*-[*m*-(α-*N*-Imidazolyl)toluamido]phenyl}-15-{*o*-[3,5-bis(ethoxycarbonyl)benzamido]phenyl}-2,8,12,18-tetraethyl-3,7,13,17-tetra-**

methylporphyrin (16). A solution of porphyrin **11** (40 mg, 0.0474 mmol) and pyridine (0.5 mL, 6.18 mmol) in methylene chloride (20 mL) was added dropwise to a well-stirred solution of 1,3,5-benzenetricarboxylic acid chloride (500 mg, 1.88 mmol) in methylene chloride (40 mL). After completion of the addition (ca. 30 min), the mixture was stirred at room temperature for 1 h. Ethanol (5 mL) was added and the reaction refluxed for 3 h. The mixture was poured into water, and the organic layer was separated and washed successively with 10% HCl (2 × 100 mL), H_2O (100 mL), $NaHCO_3$ (saturated aqueous, 100 mL), H_2O, and then dried over Na_2SO_4. After evaporation to a red oil, the product was purified on a silica gel column (2 × 25 cm). The benzene triester was eluted first with 2% HOAc–CH_2Cl_2. The protonated porphyrin was washed off the column with 5% Et_3N–CH_2Cl_2. The porphyrin containing fraction was extracted successively with 5% HCl, H_2O, $NaHCO_3$, dried over Na_2SO_4 and evaporated to dryness. Crystallization from hexane–CH_2Cl_2 yielded purple granules (30 mg, 58%).

An alternative purification method involved extraction of the crude reaction mixture into 80% phosphoric acid. The acid layer was extracted several times with methylene chloride, then diluted with water and neutralized. The neutralized suspension was back extracted with CH_2Cl_2 and the organic phase was washed with 5% HCl, H_2O, and then saturated $NaHCO_3$. The yields after chromatography on silica gel by this extraction method were generally lower than the first method.

IR: ν_{CO} 1670, 1720 cm^{-1}; NMR ($CDCl_3$) δ −2.30 (br, s, pyr-NH), 0.38 (t, 9 H, OEt), 1.73 (m, 12 H, Et), 2.58 (s, 12 H, CH_3), 3.28 (s, 2 H, $ArCH_2$), 3.37 (q, 4 H, OCH_2CH_3, 4.00 (m, 8 H, Et), 5.03 (s, 1 H, Im-H), 5.71 (s, 1 H, Im-H), 6.11 (S, 1 H, Im-H), 6.23–6.72 (m, 4 H, Ar), 7.4–8.1 (m, 11 H, Ar, NH), 8.97 (m, 2 H, Ar), 10.28 (s, 2 H, meso). Anal. Calcd for $C_{68}H_{80}N_8O_6$: C, 73.88; H, 7.30; N, 10.14. Found: C, 74.02; H, 7.43; N, 10.10.

***trans*-5-{*o*-[*m*-(α-*N*-Imidazolyl)toluamido]phenyl}-15-{*o*-[3,5-bis(*n*-butoxycarbonyl)benzamido]phenyl}-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin.** This porphyrin was prepared by the above procedure except ethanol was replaced by 1-butanol; yield from **11**: 63%. NMR ($CDCl_3$) δ −2.4 (br s, 2 H, NH), 0.50 (t, 6 H, OEt), 0.77 (m, 8 H, $BuCH_2CH_2$), 1.73 (m, 12 H, Et), 2.60 (s, 12 H, Me), 3.04 (s, 2 H, CH_2), 3.34 (t, 4 H, OEt), 4.03 (m, 8 H, Et), 5.06 (s, 1 H, Im-H), 5.67 (s, 1 H, Im-H), 6.16 (s, 1 H, Im-H), 6.2–6.6 (m, 8 H, Ar), 7.46 (d, 2 H, Ar), 7.5–8.1 (m, 6 H, Ar, NH), 8.95 (d, 2 H, Ar), 10.27 (s, 2 H, meso).

***trans*-5-{*o*-[*m*-(α-*N*-Imidazolyl)toluamido]phenyl}-15-{*o*-[3,5-bis(hydroxymethyl)benzamido]phenyl}-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin (17).** Porphyrin **16** (20 mg, 0.18 mmol) was dissolved in freshly distilled THF (25 mL). Excess lithium aluminum hydride in THF was added and the reaction stirred for 3 min at room temperature. The reaction mixture was carefully diluted with water (50 mL), followed by CH_2Cl_2 (30 mL). The organic layer was separated and washed with water, brine, and dried over Na_2SO_4. After evaporation, the mixture was separated on thick layer silica gel plates, with 5% MeOH–CH_2Cl_2. The major band was collected and lypholized from benzene to yield a red powder (13.3 mg, 70%); IR ν_{CO} 1670 cm^{-1}, ν_{OH} 3400 cm^{-1}; NMR ($CDCl_3$) δ −2.4 (br s, 2 H, pyr-NH), 1.75 (m, 12 H, Et), 2.55 (s, 6 H, CH_3), 2.59 (s, 6 H, CH_3), 3.16 (s, 4 H, $ArCH_2$), 3.25 (s, 2 H, $ArCH_2$), 3.98 (m, 8 H, Et), 5.13 (s, 1 H, Im-H), 5.69 (s, 1 H, Im-H), 5.92 (s, 2 H, Ar), 6.1–6.6 (m, 6 H, Ar), 7.4–8.1 (m, 8 H, Ar), 8.91 (m, 2 H, Ar), 10.27 (s, 2 H, meso).

***trans*-5-{*o*-[*m*-(α-*N*-Imidazolyl)toluamido]phenyl}-15-{*o*-[3,5-bis(*n*-butylaminocarbonyl)benzamido]phenyl}-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin (13).** This compound was prepared by procedures analogous to that of 3,5-diethyl ester porphyrin **16**. The crude diacid chloride was treated with excess *n*-butylamine and the resultant mixture was refluxed overnight under N_2. After purification by extraction and column chromatography, the amide was crystallized from hexane–CH_2Cl_2; 40% yield. NMR ($CDCl_3$) δ −2.4 (br s, 2 H, pyr-NH), 0.48 (t, 6 H, $BuCH_3$), 0.75 (m, 8H, $BuCH_2CH_2$), 1.73 (m, 12 H, Me), 2.58 (s, 12 H, Me), 3.23 (s, 2 H, benzyl), 3.34 (t, 4 H, CH_2O), 4.01 (m, 8 H, CH_2), 5.06 (s, 1 H, Im), 5.66 (s, 1 H, Im), 6.15 (s, 1 H, Im), 6.28 (d, 1 H, Ar), 6.40 (t, 1 H, Ar), 6.56 (m, 2 H, Ar), 7.4–8.1 (m, 11 H, Ar, NH), 8.95 (m, 2 H, Ar), 10.26 (s, 2 H, meso). Anal. Calcd for $C_{72}H_{90}N_{10}O_4$: C, 74.58; H, 7.82; N, 12.08. Found: C, 74.21; H, 7.93; N, 11.82.

***trans*-5-{*o*-[*m*-(α-*N*-Imidazolyl)toluamido]phenyl}-15-{*o*-[3,5-bis(*N*,*N*-diethylaminocarbonyl)benzamido]phenyl}-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin (14).** This was prepared as described for the diester porphyrin **16**. Excess diethylamine was added to the diacid chloride–porphyrin. After refluxing overnight under N_2 the product was purified as described; yield, 47%. NMR ($CDCl_3$) δ −2.38 (br s, 2 H, pyr-NH), −0.83 (br, 6 H, NCH_2CH_3), 0.19 (br, 6 H, NCH_2CH_3), 1.42 (br, 4 H, NCH_2), 1.74 (m, 12 H, Et), 2.24 (br, 4 H, NCH_2), 2.56 (s, 6 H, CH_3), 2.61 (s, 6 H, CH_3), 3.28 (s, 2 H, $ArCH_2$), 4.00 (m, 8 H, Et), 5.10 (s, 1 H, Im-H), 5.73 (s, 1 H, Im-H), 6.18 (s, 1 H, Im-H), 6.23–6.6 (m, 6 H, Ar), 6.68 (s, 1 H, Ar), 7.5–8.1 (m, 8 H, Ar, NH), 8.97 (m, 2 H, Ar), 10.28 (s, 2 H, meso).

***trans*-5-{*o*-[*m*-(α-*N*-Imidazolyl)toluamido]phenyl}-15-{*o*-[3,5-bis(*N*,*N*-diisopropylaminocarbonyl)benzamido]phenyl}-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin (15).** This compound was prepared by procedures identical with that for the diethyl analogue **14** except that isopropylamine was used to quench the acid chloride; yield, 55%. NMR ($CDCl_3$) δ −2.4 (br s, 2 H, pyr-NH), 1.28 (d, 12 H, *i*-Pr), 1.72 (t, 12 H, Me), 2.56 (s, 6 H, Me), 2.60 (s, 6 H, Me), 3.22 (s, 2 H, benzyl), 4.00 (m, 8 H, CH_2), 4.27 (m, 2 H, *i*-Pr), 5.04 (s, 1 H, Im), 5.65 (s, 1 H, Im), 6.14 (s, 1 H, Im); phenyl: 6.30 (d, 1 H), 6.40 (t, 1 H), 6.47 (s, 2 H), 6.54 (d, 1 H), 6.58 (s, 1 H), 6.68 (s, 1 H), 7.3–8.2 (m, 8 H, Ar, NH), 8.96 (d, 1 H), 9.03 (d, 1 H), 10.26 (s, 2 H, meso).

***trans*-5-{*o*-(*p*-*tert*-Butylbenzamido)phenyl}-15-{*o*-[3-(*N*-imidazolyl)-propylureido]phenyl}-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin (9).** To a solution of porphyrin **6** (20 mg, 0.0243 mmol) in THF (30 mL) containing pyridine (1 mL) was added an excess of phosgene in benzene (1 mL, 2.1 mmol/mL). After stirring for 20 min at room temperature, the excess phosgene was removed in vacuo. A solution of excess 3-(*N*-imidazolyl)propylamine[33] (0.5 mL, 6.7 mmol) in THF (20 mL) was added and the mixture stirred overnight. After removal of solvents, the resultant oil was redissolved in CH_2Cl_2, washed successively with 5% HCl, H_2O, and saturated $NaHCO_3$, and then dried over Na_2SO_4. The crude product was purified through a silica gel pad, crystallized from MeOH–CH_2Cl_2 to yield a purple solid (19.2 mg, 80%). NMR ($CDCl_3$) δ −0.67 (m, 2 H, CH_2), 0.72 (s, 9 H, *t*-Bu), 1.70 (t, 12 H, Et), 1.98 (m, 2 H, CH_2), 2.17 (m, 2 H, CH_2), 2.51 (s, 6 H, CH_3), 2.57 (s, 6 H, CH_3), 3.96 (q, 8 H, Et), 4.38 (t, 1 H, NH), 5.03 (s, 1 H, Im-H), 5.32 (s, 1 H, Im-H), 5.38 (s, 1 H, Im-H), 6.28 (s, 1 H, NH), 6.44 (s, 4 H, Ar), 7.36–7.94 (m, 7 H, Ar, NH), 8.57 (d, 1 H, Ar), 9.08 (d, 1 H, Ar), 10.22 (s, 2 H, meso).

***trans*-5-{*o*-(*p*-*tert*-Butylbenzamido)phenyl}-15-{*o*-[4-(*N*-imidazolyl)-butylamido]phenyl}-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin (8).** A mixture of 4-(*N*-imidazolyl)butyric acid[3b] (100 mg, 0.65 mmol) and oxalyl chloride (0.25 mL, 2.8 mmol) dissolved in acetonitrile (30 mL) was refluxed under nitrogen for 2 h. The excess oxalyl chloride and CH_3CN were removed in vacuo to yield a yellow solid. The crude acid chloride was redissolved in CH_3CN (20 mL) and added dropwise to a refluxing solution of porphyrin **6** (80 mg, 0.098 mmol) in CH_2Cl_2 (50 mL) containing triethylamine (1 mL, 7.17 mmol). After 3 h, the reaction mixture was poured into ice, the organic layer separated and washed successively with 5% HCl, H_2O, saturated $NaHCO_3$, and H_2O. After drying over Na_2SO_4, the organic layer was evaporated to dryness and the crude product purified on thick layer silica gel plates, with 3% MeOH–CH_2Cl_2. The major band was porphyrin **8**. NMR ($CDCl_3$) δ 0.75 (s, 9 H, *t*-Bu), 1.30 (m, 2 H, CH_2), 1.39 (m, 2 H, CH_2), 1.75 (t, 12 H, Et), 2.54 (s, 6 H, CH_3), 2.59 (s, 6 H, CH_3), 3.28 (t, 2 H, CH_2), 4.03 (q, 8 H, Et), 5.90 (s, 1 H, Im-H), 7.5–8.0 (m, 6 H, Ar), 8.02 (s, 1 H, NH), 8.70 (d, 1 H, Ar), 9.08 (d, 1 H, Ar), 10.30 (s, 2, meso).

***trans*-5-{*o*-(*p*-*tert*-Butylbenzamido)phenyl}-15-{*o*-[3-(*N*-imidazolyl)-propylamido]phenyl}-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin (7).** This compound was prepared by an analogous procedure as porphyrin **8**. 3-(*N*-imidazolyl)propionic acid chloride was prepared by refluxing the acid[34] and oxalyl chloride in acetonitrile for 1 h and pumped dry. The crude acid chloride was added to a methylene chloride solution of porphyrin **6** containing triethylamine. After refluxing for 2 h, the mixture was poured into ice water. The organic layer was separated, washed successively with 5% HCl, H_2O, and $NaHCO_3$, and then evaporated to dryness. The crude porphyrin was purified on preparative TLC plates (silica gel, 5% MeOH–CH_2Cl_2). NMR ($CDCl_3$) δ 0.72 (s, 9 H, *t*-Bu), 1.73 (m, 14 H, Et), 2.46 (s, 6 H, CH_3), 2.58 (s, 6 H, CH_3), 3.75 (t, 2 H, CH_2), 4.02 (m, 8 H, Et), 6.25 (s, 1 H, Im-H), 6.48 (s, 4 H, Ar), 6.63 (s, 1 H, Im-H), 6.85 (s, 1 H, NH), 7.01 (s, 1 H, Im-H), 7.56 (q, 2 H, Ar), 7.90 (m, 4 H, Ar), 8.0 (s, 1 H, NH), 8.71 (d, 1 H, Ar), 9.08 (d, 1 H), Ar), 10.29 (s, 2 H, meso).

***trans*-5-{*o*-[*m*-(α-*N*-Imidazolyl)toluamido]phenyl}-15-{*o*-(aminocarbonylacetamido)phenyl}-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin (20).** A solution of porphyrin **11** (50 mg, 0.059 mmol) in methylene chloride (30 mL) under N_2 was added to a well-stirred solution of malonyl dichloride (0.5 mL, 5.7 mmol) in CH_2Cl_2 (100 mL) and the mixture was refluxed for 2 h. At room temperature, anhydrous ammonia was bubbled through the green solution until the color changed to red. The mixture was then diluted with water (100 mL), separated, and extracted into 80% phosphoric acid (30 mL). The acid layer was washed with CH_2Cl_2 (3 × 100 mL), diluted with water, neutralized with 10%

(33) Schwan, T. J. *J. Heterocycl. Chem.* **1967**, *4*, 633.

(34) Prepared from imidazole and methyl acrylate by similar procedures described in ref 3b and 33.

NaOH, and back extracted repeatedly with CH_2Cl_2 (3 × 30 mL). The combined organic phase was washed with water (100 mL), brine (100 mL), and evaporated to dryness. The crude product was purified on silica gel plates, using 2% MeOH–CH_2Cl_2. The second band, the major band, gave the desired porphyrin which was lyophilized from benzene to yield a brown powder (11 mg, 20%). NMR ($CDCl_3$) δ −3.2 (br s, 2 H, pyr-NH), −0.45 (br s, 2 H, NH_2), 1.5 (t, 6 H, Et), 1.62 (t, 6 H, Et), 2.17 (s, 6 H, CH_3), 2.58 (s, 6 H, CH_3), 3.27 (s, 2 H, $ArCH_3$), 3.6–4.0 (m, 8 H, Et), 5.0 (s, 1 H, Im-H), 5.65 (s, 1 H, Im-H), 6.05 (s, 1 H, Im-H), 6.20 (s, 2 H, CH_2), 6.50 (s, 1 H, Ar), 7.3 (m, 2 H, Arg, NH), 7.61 (d, 1 H, Ar), 7.70 (t, 1 H, Ar), 7.80 (t, 1 H, Ar), 7.96 (t, 1 H, Ar), 7.40 (d, 1 H, Ar), 7.64 (d, 1 H, Ar), 7.94 (m, 2 H, Ar, NH), 10.0 (s, 2 H, meso).

***trans*-5-{*o*-[*m*-(α-*N*-Imidazolyl)toluamido]phenyl}-15-[*o*-((*tert*-butylamino)carbonylacetamido)phenyl]-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin (21).** This porphyrin was made in an analogous fashion as porphyrin **20**. After addition of malonyl dichloride, an excess of *tert*-butylamine was added. NMR δ −2.3 (br s, pyr-NH), 0.60 (s, 9 H, *t*-Bu), 1.70 (t, 12 H, Et), 2.34 (s, 2 H, CH_2), 2.50 (s, 6 H, CH_3), 2.60 (s, 6 H, CH_3), 3.21 (s, 2 H, $ArCH_2$), 4.00 (m, 8 H, Et), 5.11 (s, 1 H, Im-H), 5.66 (s, 1 H, Im-H), 6.0–6.6 (m, 6 H, Ar, Im-H, NH), 7.3–8.0 (m, 8 H, Ar, NH), 8.72 (d, 1 H, NH), 8.95 (d, 1 H, Ar), 10.27 (s, 2 H, meso).

***trans*-5-{*o*-[*m*-(α-*N*-Imidazolyl)toluamido]phenyl}-15-{*o*-[(dimethylamino)acetamido]phenyl}-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin (22).** This porphyrin was made in an analogous fashion as porphyrin **21**. NMR ($CDCl_3$) δ −2.35 (br s, pyr-NH), 1.00 (s, 3 H, NCH_3), 1.70 (t, 12 H, Et), 2.08 (s, 3 H, NCH_3), 2.52 (s, 6 H, CH_3), 2.59 (s, 6 H, CH_3), 2.73 (s, 2 H, $COCH_2$), 3.18 (s, 2 H, $ArCH_3$), 4.00 (m, 8 H, Et), 5.14 (s, 1 H, Im-H), 5.63 (s, H, Im-H), 6.2–6.6 (m, 5 H, Ar, Im-H), 7.5–8.0 (m, 6 H, Ar, NH), 8.2 (d, 1 H, Ar), 8.7 (m, 2 H, Ar, NH), 8.96 (d, 1 H, Ar), 10.27 (s, 2 H, meso).

***trans*-5-{*o*-[*m*-(α-*N*-Imidazolyl)toluamido]phenyl}-15-{*o*-[*m*-(α-trimethylchloroammonium)toluamido]phenyl}-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin (19).** A mixture of porphyrin **11** (40 mg, 0.0472 mmol) and excess α-bromo-*m*-toluic acid chloride (30 mg, 12.8 mmol) in methylene chloride (40 mL) was refluxed under N_2 for 90 min. The mixture was evaporated to dryness and redissolved in acetonitrile (30 mL). Excess trimethylamine (3 mL, 32.1 mmol) was added to the green solution and the reaction was stirred at room temperature for 2 h before the mixture was evaporated to dryness. The residue was redissolved in CH_2Cl_2 (30 mL), washed with H_2O (30 mL) and brine (30 mL), and then purified on silica gel plates (10% MeOH–CH_2Cl_2). The porphyrin collected from the most polar band was crystallized from CH_2Cl_2–hexane to yield a purple brown powder (33 mg, 71%). NMR ($CDCl_3$) δ −2.50 (br s, 1 H, pyr-NH), −2.37 (br s, 1 H, pyr-NH), 0.07 (s, 9 H, $N(CH_3)_3$), 1.75 (m, 12 H, Et), 2.42 (s, 2 H, $ArCH_2$), 2.58 (s, 6 H, CH_3), 2.63 (s, 6 H, CH_3), 3.55 (s, 2 H, $ArCH_2$), 4.04 (m, 8 H, Et), 4.32 (s, 1 H, Ar), 5.21 (s, 1 H, Im-H), 5.98 (s, 1 H, Im-H), 6.15 (s, 1 H, Im-H), 6.39 (s, 3 H, Ar), 6.63 (s, 1 H, Ar), 6.90 (t, 1 H, Ar), 7.16 (d, 1 H, Ar), 7.4 (m, 2 H, Ar), 7.7 (m, 2 H, Ar), 7.94 (m, 2 H, Ar), 8.12 (d, 1 H, Ar), 8.86 (d, 1 H, Ar), 8.97 (d, 1 H, Ar), 10.34 (s, 2 H, meso).

3,5-Bis(bromomethyl)benzoic Acid. A mixture of 3,5-dimethylbenzoic acid (12.5 g, 83 mmol), *N*-bromosuccinimide (29.7 g, 163 mmol), and benzoyl peroxide (0.2 g) in CCl_4 (200 mL) was refluxed vigorously. The progress of reaction was monitored by NMR. After 3 h, the mixture was cooled and the solid was filtered and washed with CCl_4. The filtrate was evaporated to dryness to yield a yellow solid and recrystallized in MeOH–CH_2Cl_2 to give an off-white powder (9.75 g, 38% yield). NMR ($CDCl_3$–acetone-d_6) δ 4.5 (s, 4 H, CH_2), 7.6 (t br s, 1 H, Ar), 8.0 (br s, 2 H, Ar); MS *m/e* 309, 307, 305.

***trans*-5-{*o*-[*m*-(α-*N*-Imidazolyl)toluamido]phenyl}-15-{*o*-[3,5-bis(methoxymethyl)benzamido]phenyl}-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin (18).** To a suspension of 3,5-bis(bromomethyl)benzoic acid (500 mg, 1.62 mmol) in CH_2Cl_2 (50 mL) was added an excess of thionyl chloride (0.5 mL, 6.8 mmol). The solution was refluxed for 6 h, after which the excess $SOCl_2$ and CH_2Cl_2 was removed in vacuo to yield a yellow solid.

A portion of the crude acid chloride (100 mg, 0.3 mmol) dissolved in CH_2Cl_2 (20 mL) was added dropwise to a solution of porphyrin **8** (50 mg, 0.059 mmol) in CH_2Cl_2 (50 mL). After refluxing under N_2 for 3 h, the solvent was removed and the green solid was redissolved in methanol (40 mL). Sodium hydride (20 mg, 0.86 mmol) was slowly added and the solution refluxed for 2 h. After removal of the methanol, the residue was redissolved in CH_2Cl_2 (50 mL) and successively washed with water (100 mL), 5% HCl (100 mL), H_2O (100 mL), $NaHCO_3$ (saturated aqueous, 100 mL), and H_2O. Purification through a silica gel pad (5% MeOH–CH_2Cl_2) and crystallization from hexane–CH_2Cl_2 afforded 38 mg of the porphyrin (64% yield). NMR ($CDCl_3$) δ −2.3 (br s, pyr-NH), 1.75 (q, 12 H, Et), 2.26 (s, 6 H, OCH_3), 2.57 (s, 6 H, CH_3), 2.59 (s, 6 H, CH_3), 3.12 (s, 4 H, $ArCH_2$), 3.25 (s, 2 H, $ArCH_2$), 4.00 (m, 8 H, Et), 5.11 (s, 1 H, Im-H), 5.67 (s, 1 H, Im-H), 6.1–6.7 (m, 8 H, Ar), 7.5–8.1 (m, 6 H, Ar, NH), 8.96 (m, 2 H, Ar), 10.30 (s, 2 H, meso).

***trans*-5-[*o*-(*p*-*tert*-Butylbenzamido)phenyl]-15-{*o*-[γ-bis((ethoxycarbonyl)methyl)aminobutyramido]phenyl}-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin (25).** A mixture of *t*-Boc-aminobutyric acid (155 mg) and triethylamine (100 mg) in dry toluene (15 mL) was cooled to 0 °C under nitrogen. A solution of ethyl chloroformate (75 mg) in toluene (10 mL) was added dropwise and the solution was allowed to warm to room temperature. The *t*-Bu porphyrin **6** (100 mg) in dry THF (20 mL) was added, followed by refluxing for 3 h. The solvent was removed in vacuo and the residue redissolved in CH_2Cl_2 and washed successively with 10% HCl, H_2O, and aqueous $NaHCO_3$. Purification was done on protonated silica gel columns using 10% acetic acid/CH_2Cl_2 to elute unreacted amino acid. The desired *t*-Boc-aminobutyramide porphyrin was eluted with 10% methanol/CH_2Cl_2. NMR ($CDCl_3$) confirmed the presence of the *t*-Boc group: δ 0.96.

The *t*-Boc group was removed by dissolving the above porphyrin in acetic acid (20 mL) containing HCl (2 mL) and stirring at room temperature for 10 min. The resultant amino porphyrin was treated with an excess ethyl bromoacetate (1 mL) in CH_2Cl_2 (10 mL) and acetonitrile (10 mL) containing Et_3N (1 mL). The mixture was refluxed for 1.5 h and the product was purified on silica gel TLC plates. NMR ($CDCl_3$) δ −2.37 (br s, 2 H, NH), 0.63 (t, 6 H, OEt), 0.74 (s, 12 H, *t*-Bu), 1.27 (m, 2 H, CH_2), 1.52 (t, 2 H, CH_2), 1.76 (m, 12 H, Me), 2.03 (t, 2 H, CH_2), 2.57 (s, 6 H, Me), 2.59 (s, 6 H, Me), 2.71 (s, 4H, CH_2), 3.21 (q, 4 H, OEt), 4.03 (m, 8 H, CH_2), 6.47 (s, 4 H, Ar), 7.26 (s, 1 H, NH), 7.48 (m, 2 H, Ar), 7.5–7.9 (m, 4 H, Ar), 8.0 (s, 1 H, NH), 8.77 (d, 1 H, Ar), 9.09 (d, 1 H, Ar), 10.28 (s, 2 H, meso).

Methyl 2-(Carboxylacetyl)pyridine-6-carboxylate (23). Methyl 2-carboxypyridine-6-carboxylate (2-methyl dipicolinate) was prepared from dipicolinic acid via the silver salt according to Ooi and Magee.[27] The monoacid monoester (3 g) suspended in benzene was treated with an excess of thionyl chloride (10 mL). The mixture was stirred at 50 °C for 8 h until all the solids became dissolved. The solution was evaporated to dryness and the resultant acid chloride, *m/e* 200, was used without further purification.

Methyllithium (28.5 mL, 1.4 M) was added dropwise to a solution of bis(trimethylsilyl) malonate (9.64 g, 38.9 mmol) in ether (77 mL) under argon at −78 °C. Following the addition, the solution was allowed to warm to 0 °C, and the above acid chloride (3.8 g, 19 mmol) dissolved in THF (40 mL) was added. The solution was stirred for 10 min and a cold aqueous solution of $NaHCO_3$ (5%, 200 mL) was added. The mixture was thoroughly shaken before the aqueous layer was separated. It was acidified to pH 2 with cold 4 N H_2SO_4, then extracted repeatedly with ether (100 mL × 3). The organic phase was separated, dried, and evaporated to give the keto acid. Decarboxylated impurities (mostly 2-acetylpicolinate) were removed by washing with cold ether. The keto acid was crystallized from CH_2Cl_2 to give white needles (2 g, 47%); mp 120–121 °C; NMR ($CDCl_3$–acetone-d_6) δ 3.95 (s, 3 H, OMe), 4.20 (s, 2 H, CH_2), 8.20 (m, 4 H, Py); MS *m/e* 179 ($M^+ - CO_2$).

***trans*-5-[*o*-(*p*-*tert*-Butylbenzamido)phenyl]-15-{*o*-[2-(((6-methoxycarbonyl)pyridyl)carbonyl)acetamido]phenyl}-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin (24).** To a solution of porphyrin **6** (20 mg, 0.025 mmol) in CH_2Cl_2 (50 mL) was added an excess of the β-keto acid (22.3 mg, 0.1 mmol) and DCC (20.6 mg, 0.1 mmol). The solution was allowed to stir at room temperature for 3 h or until completion of the reaction as indicated by TLC. Water was added and the organic layer separated, washed successively with 10% HCl, water, 5% NaOH, and dried. After evaporation, the crude solid was crystallized from CH_2Cl_2–hexane to afford a red powder, yield: 23 mg, 94%; mp 250 °C. NMR (toluene-d_8) δ −3.1 (br s, 1 H, NH), −2.1 (br s, 1 H, NH), 0.28 (s, 9 H, *t*-Bu), 1.70 (t, 6 H, Me), 2.53 (s, 6 H, Me), 2.77 (s, 6 H, Me), 3.00 (s, 3 H, OMe), 3.08 (t, 1 H, py), 3.50 (s, 2 H, CH_2), 3.58 (d, 1 H, py), 3.80 (m, 8 H, CH_2), 5.21 (d, 1 H, py), 5.87 (d, 2 H, Ar), 6.46 (d, 2 H, Ar), 7.23 (t, 1 H, Ar), 7.35 (t, 1 H, Ar), 7.48 (d, 1 H, Ar), 7.60 (t, 1 H, Ar), 7.74 (t, 1 H, Ar), 7.82 (d, 1 H, Ar), 8.12 (s, 1 H, Ar), 8.68 (d, 1 H, Ar), 8.72 (s, 1 H, NH), 9.57 (d, 1 H, Ar), 10.29 (s, 2 H, meso). Anal. Calcd for $C_{65}H_{67}N_7O_5$: C, 76.07; H, 6.58; N, 9.55. Found: C, 76.11; H, 6.38; N, 9.32.

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Registry No. 1a, 94111-50-9; **1a** (diacetamide, FeCl complex), 94111-49-6; **1b**, 94160-65-3; **1b** (diacetamide), 94136-32-0; **2**, 92415-30-0; **2**·2Na, 94111-51-0; **3**, 94136-30-8; **3** (porphyrin), 94111-71-4; **4a**, 94111-80-5; **4a** (FeCl complex), 94111-46-3; **4a** (FeOFe complex), 94111-47-4; **5a**, 94233-44-0; **5a** (FeCl complex), 94160-64-2; **5a** (FeOH

complex), 94111-48-5; **6**, 94111-53-2; **7**, 94111-54-3; **8**, 94111-55-4; **9**, 94111-56-5; **10**, 94111-57-6; **11**, 94111-58-7; **12a**, 94160-66-4; *cis*-**12a**, 94111-52-1; **13**, 94111-59-8; **13** (diacid chloride), 94111-73-6; **14**, 94111-60-1; **15**, 94111-61-2; **16**, 94136-31-9; **16** (dibutyl ester), 94111-72-5; **17**, 94111-62-3; **18**, 94111-63-4; **19**, 94111-64-5; **20**, 94111-65-6; **21**, 94111-66-7; **22**, 94111-67-8; **23**, 94111-68-9; **24**, 94111-69-0; **25**, 94111-70-3; o-$O_2NC_6H_4CHO$, 552-89-6; p-t-$BuC_6H_4CO_2H$, 98-73-7; p-t-BuC_6H_4COCl, 1710-98-1; m-$MeC_6H_4CO_2H$, 99-04-7; m-$BrCH_2C_6H_4CO_2H$, 6515-58-8; m-$BrCH_2C_6H_4COCl$, 54267-06-0; 1,3,5-$C_6H_3(COCl)_3$, 4422-95-1; $Im(CH_2)_3NH_2$, 5036-48-6; $Im(CH_2)_3CO_2H$, 72338-58-0; $Im(CH_2)_3COCl$, 66188-79-2; $Im(CH_2)_2CO_2H$, 18999-45-6; $Im(CH_2)_2COCl$, 94111-74-7; $CH_2(COCl)_2$, 1663-67-8; t-$BuNH_2$, 75-64-9; 3,5-$Me_2C_6H_3CO_2H$, 499-06-9; 3,5-$(BrCH_2)_2C_6H_3CO_2H$, 94111-75-8; 3,5-$(BrCH_2)_2C_6H_3COCl$, 94111-76-9; t-$BocNH(CH_2)_3CO_2H$, 57294-38-9; $BrCH_2CO_2Et$, 105-36-2; $CH_2(CO_2SiMe_3)_2$, 18457-04-0; 5,5′-bis(ethoxycarbonyl)-4,4′-diethyl-3,3′-dimethyl-2,2′-dipyrrylmethane, 6305-93-7; *trans*-5-[*o*-(*p*-*tert*-butylbenzamido)phenyl]-15-[*o*-[γ-(*tert*-butoxycarbonylamino)butyramido]phenyl]-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin, 94111-77-0; *trans*-5-[*o*-(*p*-*tert*-butylbenzamido)phenyl]-15-[*o*-(γ-aminobutyramido)phenyl]-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin, 94111-78-1; 2-methyl dipicolinate, 7170-36-7; 2-methyl dipicolinic monochloride, 94111-79-2.

Hexacyclen Complexes of Anions. 2. Bonding Forces, Structures, and Selectivity

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Abstract: Anion binding properties of hexacyclen ($C_{12}H_{30}N_6$) with $C_6H_5SO_3^-$, $CF_3CO_2^-$, ClO_4^-, and IO_3^- are studied by pH potentiometry and ^{13}C NMR. In each case tetraprotonated hexacyclen, H_4L^{4+}, is the sole complexing macrocycle species. Each anion forms a 1:1 complex with H_4L^{4+}, but a novel 1:2 stoichiometry is detected with IO_3^-. Temperature-dependent binding constants are derived for each complexation in the range from 15 to 55 °C. van't Hoff analyses provide estimates of enthalpy and entropy changes for each reaction. These data are interpreted in terms of solvent ordering by the H_4L^{4+} species as providing the driving force in these reactions, while anion steric properties seem not to play an important role.

1,4,7,10,13,16-Hexaazacyclooctadecane, to be referred to as hexacyclen, L, is a macrocyclic polyamine capable of complexing anions in aqueous solution (Figure 1). Although complexation reactions of this type hve been discovered only recently, several investigations[1-3] have been reported already. In most cases it appears that highly protonated forms of the polyamines participate in the complexation reactions and involve 1:1 anion-to-macrocycle stoichiometries. Some studies report anion complexation by tetra-, hexa-, and octa-protonated macrocyclic polyamines.[4] Some of us[5] describe exclusive 1:1 stoichiometries in tetraprotonated hexacyclen, H_4L^{4+}, with nitrate, chloride, perchlorate, and bromide ions but find no detectable complexation between these anions and other protonated hexacyclen species.

It has generally been assumed that electrostatic and ionic–hydrogen bonding interactions provide the bonding forces in anion complexes of protonated macrocyclic polyamines while the size and shape of the macrocycle cavity account for bonding selectivity. In ref 5, however, we suggest that solvent release is an important driving force in these reactions. This inference is based on the thermodynamic parameters ΔH and ΔS for the H_4L^{4+} complexation reactions of chloride and nitrate ions as well as an X-ray crystallographic analysis of a number of hexacyclen salts, including the tetrahydrochloride, tetrakis(hydrogen nitrate), and di(hydrogen nitrate) dihydrochloride.

Our present purpose is to obtain further information on the thermodynamic properties of hexacyclen complexation of anions in order to elucidate the solvent's role in these reactions. In order to obtain the experimental data necessary to this investigation we employ a pH potentiometric method to estimate the temperature-dependent formation constants of H_4L^{4+} with trifluoroacetate, benzenesulfonate, perchlorate, and iodate anions. In the course of this work we also determined a novel stoichiometry between H_4L^{4+} and iodate anions which features both 1:1 and 1:2 H_4L^{4+}:iodate complexes. We begin with a description of experimental methods.

Experimental Section

Materials. All chemicals were reagent grade. Sodium benzenesulfonate was found to contain trace quantities of weakly acidic impurities and was purified by repeated crystallization from 1:1 ethanol/water mixtures. The vacuum-dried product yielded essentially neutral aqueous solutions even at concentrations of 0.4 F. pH potentiometric measurements made with these solutions during addition of small amounts of HCl or NaOH indicated the absence of acidic or basic impurities even at the 0.05 mF level. Commercial sodium perchlorate, trifluoroacetate, and iodide-free sodium iodate were similarly tested and found to be free of interfering acidic or basic impurities.

Hexacyclen hexahydrochloride and hexakis(hydrogen nitrate) salts were prepared as follows: Weighed portions of the commercial tris(dihydrogen sulfate) salt from Parish Chemical Co. were dissolved in water (~0.5 F) and treated with an equivalent amount of $BaCO_3$. After being mixed for 2 h at 80 °C, the filtered hot solution was concentrated with a rotary evaporator and treated with a large excess of mineral acid. The product was recrystallized from a fresh portion of the 6 F acid and air dried. Crystalline samples of $C_{12}H_{30}N_6 \cdot 6HCl \cdot 3H_2O$ ($H_6LCl_6 \cdot 3H_2O$) and $C_{12}H_{30}N_6 \cdot 6HNO_3 \cdot H_2O$ ($H_6L(NO_3)_6 \cdot H_2O$) were obtained. Solutions were prepared directly from these samples and analyzed by pH potentiometric titration with 0.1 F NaOH in the presence of 0.4 F $NaNO_3$. Under these conditions both $a = 2$ and $a = 3$ (mol of NaOH/mol of hexacyclen) end points are discernible and these end points provided a direct estimate of hexacyclen concentration. $a = 2.5$ hexacyclen solutions were prepared by addition of NaOH solutions to the analyzed stock. Because microbial growth appeared in these solutions after a few days, the solutions were used immediately or were preserved by adding a droplet of chloroform and refrigerating. This preservation practice had no discernible effect on the pH value.

Tetrakis(aminomethyl)methane was prepared by previously described methods.[6] Purified samples of the tetrahydrochloride were employed to

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