Synthesis of PDK, a Novel Porphyrin-Linked Dicarboxylate Ligand

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A novel trinucleating ligand system H_4(PDK), for porphyrin-based diamine bis(Kemp's triacid)-imide, was constructed by using two molecules of Kemp's triacid and one molecule of porphyrin as building blocks. The dimeso-substituted octaalkylporphyrin unit, carrying bromomethyl groups at the ortho positions of two trans-positioned *meso*-phenyl groups, was synthesized from (3,3′-diethyl-4,4′-dimethyl-2,2′-dipyrrolyl)methane and α-bromo-*o*-tolualdehyde. The structures of both of the two atropisomers (α,α- and α,*β*-) of bromoporphyrin, H_2(α,α-BP) and H_2(α,*β*-BP), were determined by X-ray crystallography, with the α,*β*-isomer as the free base form and the α,α-isomer as the zinc complex. Both the α,α- and α,*β*-isomers of the bromomethyl porphyrins were converted to their aminomethyl derivatives, H_2(α,α-AP) and H_2(α,*β*-AP), through the corresponding imidoporphyrin intermediates, H_2(α,α-IP) and H_2(α,*β*-IP), by the Gabriel synthesis. The α,α- and α,*β*- aminoporphyrins were coupled with Kemp's triacid anhydride-chloride to form H_4(α,α-PDK) and H_4(α,*β*-PDK), respectively. Unlike the α,*β*-isomer, the structure of which was determined by X-ray crystallography for the zinc complex, H_4(α,α-PDK) has a remarkable and complicated solvent-dependent ^{1}H NMR spectrum that suggests the existence of hydrogen bonding interactions between two convergent, tethered Kemp's triacid units, as predicted in a modeling study. The convergent feature is essential for the target ligand H_4(α,α-PDK) to form trinuclear metal complexes with a bis(carboxylato) dimetallic unit sitting above a metalloporphyrin ring.

Introduction

Metal ions play a significant role in biological transformations, as established through the discovery of numerous metalloenzymes and studies of their structures and functions.[1] Among the many chemical transformations mediated by metalloenzymes are multielectron redox reactions such as the activation of O_2. These processes are among the most important and challenging to understand. Structural and mechanistic information obtained through a variety of spectroscopic and X-ray crystallographic studies reveals that two or more metal ions are required at the active centers of many multielectron redox enzymes. Significant examples include heme-iron enzymes such as cytochrome P-450[2,3] and non-heme diiron enzymes such as soluble methane monooxygenase (sMMO) and ribonucleotide reductase (RNR).[4] These proteins have the ability to activate dioxygen through multielectron reduction to accomplish substrate oxidation, for example, the hydroxylation of alkanes. Considerable progress has been made in the synthesis of metalloporphyrins and dinuclear metal complexes having structures analogous to those of the active sites of cytochrome P-450[5,6] and non-heme diiron enzymes.[4,7,8]

The utility of Kemp's triacid[9,10] as a building block, not only for molecular receptors[11,12] but also for metal chelating ligands, has been demonstrated in recent years. The ligand XDK, where H_2(XDK) denotes *m*-xylenediamine bis(Kemp's triacid imide), is assembled by condensation of two Kemp's triacid anhydride-chloride molecules with *m*-xylenediamine as a spacer.[13] XDK has proved effective for preparing dinuclear metal complexes including non-heme diiron enzyme models.[14−22] Several porphyrin derivatives containing a Kemp's triacid moiety have been synthesized as host molecules for the purpose of molecular recognition.[23−26] The porphyrin unit in these

(1) Lippard, S. J.; Berg, J. M. *Principles of Bioinorganic Chemistry*; University Science Books: Mill Valley, CA 94941, 1994.
(2) Guengerich, F. P.; Macdonald, T. J. *Acc. Chem. Res.* **1984**, *17*, 9.
(3) Groves, J. T.; Watanabe, Y. *J. Am. Chem. Soc.* **1988**, *110*, 8443.
(4) Feig, A. L.; Lippard, S. J. *Chem. Rev.* **1994**, *94*, 759.
(5) Mansuy, D. *Coord. Chem. Rev.* **1993**, *125*, 129.
(6) Meunier, B. *Chem. Rev.* **1992**, *92*, 1411.
(7) Que, L., Jr.; Dong, Y. *Acc. Chem. Res.* **1996**, *29*, 190.
(8) Que, L., Jr.; True, A. E. *Prog. Inorg. Chem.* **1990**, *38*, 97.
(9) Kemp, D. S.; Petrakis, K. S. *J. Org. Chem.* **1981**, *46*, 5140.
(10) Rebek, J., Jr.; Askew, B.; Killoran, M.; Nemeth, D.; Lin, F.-T. *J. Am. Chem. Soc.* **1987**, *109*, 2426.
(11) Rebek, J., Jr. *Science* **1987**, *235*, 1478.
(12) Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 245.
(13) Rebek, J., Jr.; Marshall, L.; Wolak, R.; Parris, K.; Killoran, M.; Askew, B.; Nemeth, D.; Islam, N. *J. Am. Chem. Soc.* **1985**, *107*, 7476.
(14) Tanase, T.; Watton, S. P.; Lippard, S. J. *J. Am. Chem. Soc.* **1994**, *116*, 6, 9401.
(15) Yun, J. W.; Tanase, T.; Pence, L. E.; Lippard, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 4407.
(16) Tanase, T.; Lippard, S. J. *Inorg. Chem.* **1995**, *34*, 4682.
(17) Tanase, T.; Yun, J. W.; Lippard, S. J. *Inorg. Chem.* **1995**, *34*, 4220.
(18) Goldberg, D. P.; Watton, S. P.; Massachelein, A.; Wimmer, L.; Lippard, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 5346.
(19) Watton, S. P.; Masschelein, A.; Rebek, J., Jr.; Lippard, S. J. *J. Am. Chem. Soc.* **1994**, *116*, 5196.
(20) Herold, S.; Pence, L. E.; Lippard, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 6134.
(21) Hagen, K. S.; Lachicotte, T.; Kitaygorodskiy, A.; Elbouadili, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1321.
(22) LeCloux, D. D.; Barrios, A. M.; Mizoguchi, T. J.; Lippard, S. J. *J. Am. Chem. Soc.* **1998**, *120*, 9001−9014.
(23) Liang, Y.; Chang, C. K. *Tetrahedron Lett.* **1995**, *36*, 3817.
(24) Chang, C. K.; Liang, Y.; Aviles, G.; Peng, S.-M. *J. Am. Chem. Soc.* **1995**, *117*, 4191.
(25) Lindsey, J. S.; Kearney, P. C.; Duff, R. J.; Tjivikua, P. T.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1988**, *110*, 6575.

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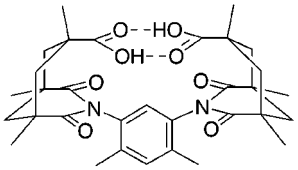
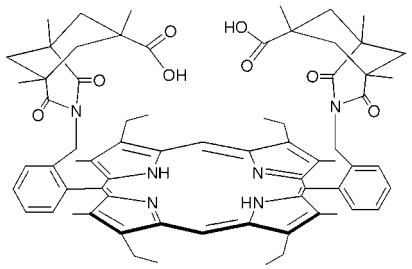
compounds served only as a spacer and/or a molecular receptor site, however, and there is no prior example of a multinuclear metal complex using a porphyrin-linked Kemp's triacid as the ligand.



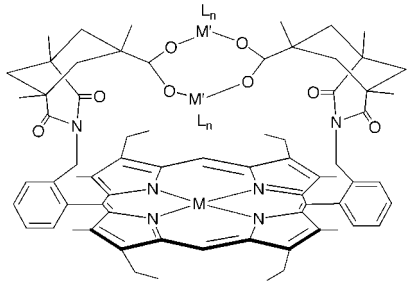
H_2(XDK)

In our continuing program to achieve a functional model for sMMO,[19,22,27,28] we were interested in designing and constructing a system that can accommodate the essential features of both the hydroxylase (MMOH) and the reductase (MMOR) component proteins of sMMO.[4,29] Substitution of the *m*-xylylenediamine spacer of XDK with a porphyrin unit afforded a model that contains the bis(carboxylato) diiron core of MMOH supported and protected by a redox-active metalloporphyrin moiety for assisting in the reductive activation of dioxygen, like the function of MMOR. Although constructs linking a metalloporphyrin to a second metal-binding unit were available[30−36] as synthetic models related to cytochrome *c* oxidase, there was no prior example of a triiron complex having both heme and dinuclear non-heme iron features in a molecule. Such an assembly facilitates comparison of the active site chemistry in these two major metalloenzyme classes and also offers the potential to observe new reactivities.

To achieve this goal, we introduced[37] the ligand PDK, where H_4(α,α-PDK) is α,α-5,15-bis(α-*N*-(Kemp's triacid imido)-*o*-tolyl)-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin, derived from one porphyrin unit and two convergent, tethered Kemp's triacid units. The reaction of H_4(α,α-PDK) with $FeBr_2$ in the presence of 2,6-lutidine produced a novel triiron(II) complex [Fe_3(α,α-PDK)(Lut)-$(Br)_2$(HBr)] in which a neutral HBr molecule resides in the cavity housing three ferrous ions in an unprecedented binding mode.[37] A similar triiron(II) complex [Fe_3(α,α-PDK)(Lut)$(I)_2$(HI)] with essentially the same geometry was obtained when FeI_2 was used as the iron source. Here we report the design and synthetic details for preparing this novel porphyrin-linked dicarboxylate ligand. The chemistry used in several of the individual steps is potentially applicable to the synthesis of related molecules.



H_4(α,α-PDK)



[MM'_2L_n(α,α-PDK)]

Results and Discussion

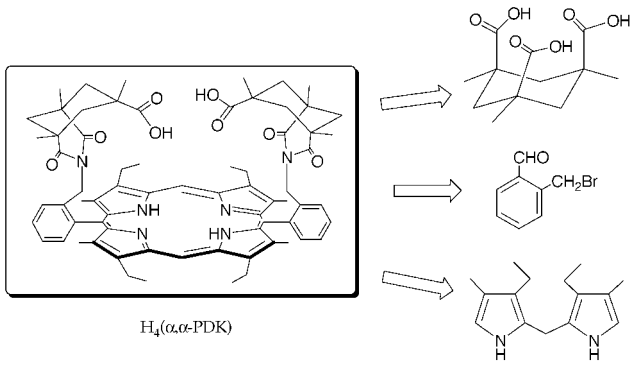
Ligand Design. The target ligand 5,15-bis(α-*N*-(Kemp's triacid imido)-*o*-tolyl)-2,8,12,18-tetraethyl-3,7,-13,17-tetramethylporphyrin (H_4(α,α-PDK)) was constructed from three pairs of building blocks, Kemp's triacid, α-bromo-*o*-tolualdehyde and dipyrrolylmethane as indicated in the retrosynthetic analysis (Scheme 1). The choice of (3,3′-diethyl-4,4′-dimethyl-2,2′-dipyrrolyl)-methane for the porphyrin synthesis was based on several considerations which are key elements in the ligand design. Compared with tetraarylporphyrins, octaalkylporphyrins are more soluble in organic solvents, allowing separation of atropisomers to be achieved on a relatively large scale by column chromatography. The isolated atropisomers are stable toward interconversion in subsequent reaction steps owing to steric interactions between the meso substituted phenyl rings and the methyl groups on the pyrroles. Moreover, these ethyl and methyl groups serve as convenient spectroscopic markers for product characterization by ^{1}H NMR spectroscopy.

The synthetic route to H_4(α,α-PDK) is outlined in Scheme 2. The synthesis takes advantage of Rebek's well-tested coupling reaction between Kemp's triacid anhydride-chloride and a diamine, a procedure used in the synthesis of H_2(XDK).[13] The porphyrin-based diamine H_2(AP) was obtained from the dibromo derivative H_2(BP) by Gabriel synthesis (Scheme 2). The dibromoporphyrin H_2(BP) was constructed from α-bromo-*o*-tolualdehyde and (3,3′-diethyl-4,4′-dimethyl-2,2′-dipyrrolyl)methane as illustrated.

Synthesis of Building Blocks. There is only a single report in the literature[38] on the synthesis of the very simple substituted aromatic aldehyde, α-bromo-*o*-tolualdehyde, a four-step route starting from *o*-tolualdehyde with a total yield of only 5.6%. The number of steps and poor yield of this synthesis are in striking contrast to the one-step, high yield syntheses of both α-bromo-*p*-tolualdehyde[39] and α-bromo-*m*-tolualdehyde[40] from their nitrile

(26) Shipps, G., Jr.; Rebek, J., Jr. *Tetrahedron Lett.* **1994**, *35*, 6823.
(27) Lee, D.; Lippard, S. J. *J. Am. Chem. Soc.* **1998**, *120*, 12153.
(28) Herold, S.; Lippard, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 145.
(29) Gassner, G. T.; Lippard, S. J. *Biochemistry* **1999**, *38*, 12768.
(30) Ju, T. D.; Ghiladi, R. A.; Lee, D.-H.; Strijdonck, G. P. F. v.; Woods, A. S.; Cotter, R. J.; Victor G. Young, J.; Karlin, K. D. *Inorg. Chem.* **1999**, *38*, 2244−2245.
(31) Collman, J. P.; Schwenninger, R.; Rapta, M.; Bröring, M.; Fu, L. *Chem. Commun.* **1999**, *2*, 137−138.
(32) Martens, C. F.; Murthy, N. N.; Obias, H. V.; Karlin, K. D. *Chem. Commun.* **1996**, 629.
(33) Nanthakumar, A.; Fox, S.; Karlin, K. D. *J. Chem. Soc., Chem. Commun.* **1995**, 499.
(34) Collman, J. P.; Fu, L.; Herrmann, P. C.; Zhang, X. *Science* **1997**, *275*, 949.
(35) Lee, S. C.; Holm, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 5833.
(36) Karlin, K. D.; Nanthakumar, A.; Fox, S.; Murthy, N. N.; Ravi, N.; Huynh, B. H.; Orosz, R. D.; Day, E. P. *J. Am. Chem. Soc.* **1994**, *116*, 4753.
(37) Zhang, X.-X.; Fuhrmann, P.; Lippard, S. J. *J. Am. Chem. Soc.* **1998**, *120*, 10260.
(38) Norcross, B. E.; Lansinger, J. M.; Martin, R. L. *J. Org. Chem.* **1977**, *42*, 369.
(39) Lavallee, D. K.; Xu, Z.; Pina, R. *J. Org. Chem.* **1993**, *58*, 6000.

Scheme 1



precursors by the controlled reduction with diisobutylaluminum hydride (DIBAL-H). Initial attempts to prepare α-bromo-*o*-tolualdehyde by DIBAL-H reductions of α-bromo-*o*-tolunitrile gave poor yields (6−20%) with difficulty of purification, owing to the formation of a large amount of black polymeric material during the hydrolysis step. A variety of conditions were then examined, including different solvents, temperatures and workup procedures. The black polymeric material presumably arises from acidic polymerization of the unstable isoindole, which is formed following by intramolecular nucleophilic attack on the *o*-bromomethyl functional group by the electron-rich nitrogen atom in the intermediate ($-CH{=}N^{-}\text{-}Al^{+}R_2$). This reaction, which is obviously impossible in the reduction of α-bromo-*p*-tolunitrile and α-bromo-*m*-tolunitrile, competes with hydrolysis for producing the desired compound, α-bromo-*o*-tolualdehyde in the case of α-bromo-*o*-tolunitrile. To avoid this undesired intramolecular reaction, a different workup procedure was employed. Specifically, the reaction mixture was poured directly into a suspension consisting of ice and an aqueous HBr solution instead of adding the acid into the reaction mixture. The use of aqueous HBr solution rather than HCl avoids formation of α-chloro-*o*-tolualdehyde obtained when the latter was used, presumably resulting via a halide exchange reaction. With the new workup procedure, the α-bromo-*o*-tolualdehyde building block was synthesized as a clear brown liquid in 97% yield (Scheme 2).

Both (3,3′-diethyl-4,4′-dimethyl-2,2′-dipyrrolyl)methane and Kemp's triacid anhydride-chloride were synthesized by following modified literature precedues. The former was prepared from commercially available [5,5′-bis(ethoxycarbonyl)-3,3′-diethyl-4,4′-dimethyl-2,2′-dipyrrolyl]methane through hydrolysis and decarboxylation steps[41,42] (Scheme 2). Kemp's triacid anhydride-chloride was made from 1,3,5-cyclohexanetricarboxylic acid in a four-step synthesis.[9,10,13]

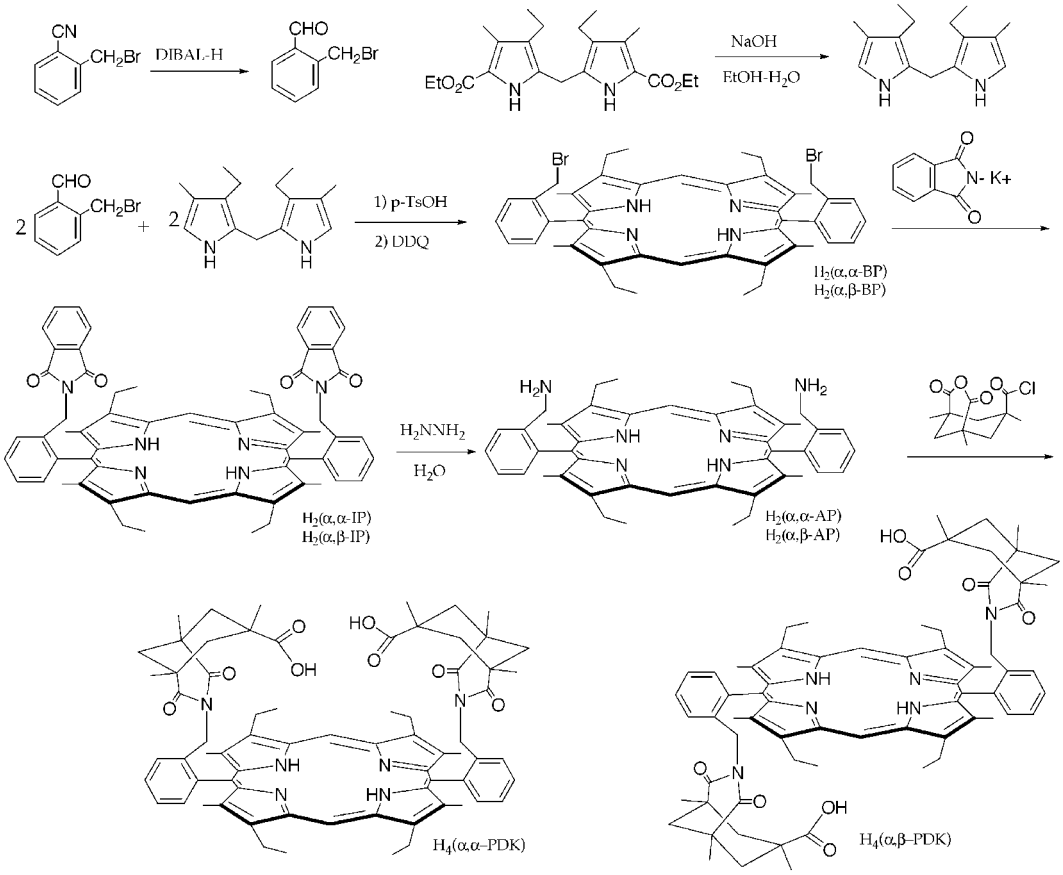
Construction of the Porphyrin Unit. Initially, the bromoporphyrin, 5,15-bis(α-bromo-*o*-tolyl)-2,8,12,18-tetraethyl-3,7,13,17-tetramethyl porphyrin, H_2(BP), was synthesized by a one-pot method[43] without isolation of the porphyrinogen cyclization intermediate. The reaction was carried out at room temperature in anhydrous acetonitrile with trichloroacetic acid as the catalyst, followed by in situ oxidation with *p*-chloranil. Porphyrin H_2(BP) was obtained in good yield (45%) as a mixture of α,α- and α,*β*-atropisomers, H_2(α,α-BP) and H_2(α,*β*-BP), in a 35:65 ratio as determined by ^{1}H NMR integration. This one-pot procedure only worked satisfactorily in a small-scale synthesis, however. It gave a poor yield (∼10%) and was difficult to purify when a relatively large-scale synthesis was carried out, due to formation of a large amount of polymeric material. A two-step approach[41,44] was then employed with the isolation of the intermediate porphyrinogen (Scheme 2). A gram scale synthesis of pure porphyrin H_2(BP) was achieved in 36% yield when methanol was used as the solvent and *p*-toluenesulfonic acid as the catalyst. The porphyrinogen intermediate precipitated out from methanol and was easily isolated by filtration. Subsequent DDQ oxidation afforded porphyrin H_2(BP) as a 45:55 mixture of α,α- and α,*β*-atropisomers, H_2(α,α-BP) and H_2(α,*β*-BP).

The atropisomers were separated by flash chromatography on a silica gel column, eluting with a solvent mixture composed of 50% (v:v) of ethyl acetate and hexane. The ^{1}H NMR spectra of the H_2(α,α-BP) and H_2-(α,*β*-BP) isomers displayed the same peak pattern. As a result, the isomeric structures could not be determined based on NMR spectroscopy. The higher R_f fraction of the reaction mixture, which eluted first from the column, was initially assigned as the α,*β*-isomer H_2(α,*β*-BP) based on its lower polarity. The more polar, lower R_f fraction, which eluted with CH_2Cl_2 after the first fraction was collected, was assigned as the α,α-isomer H_2(α,α-BP). Once the isolated atropisomers were available, however, we found that they had very different solubility properties. Whereas the less polar, higher R_f fraction was quite soluble in diethyl ether, the more polar, lower R_f fraction was completely insoluble in the same solvent. This solubility difference provided an easier separation method for the two isomers, which could be later converted to an equilibrium mixture at elevated temperature to increase the yield of the desired isomer. The UV−vis spectra of H_2(α,α-BP) and H_2(α,*β*-BP) are similar and exhibit the characteristic porphyrin Soret and Q-bands.

Identification of atropisomers of porphyrins based on polarity is commonly used in the literature, because of their indistinguishable NMR spectra.[42,44,45] The less polar α,*β*-isomer is expected to elute first from silica gel using organic solvents as the eluant, followed by the more polar α,α-isomer. In this case, however, X-ray crystallography proved such an assignment for H_2(α,α-BP) and H_2(α,*β*-BP) based on polarity to be incorrect. Single crystals of the lower R_f isomer suitable for X-ray diffraction were grown by vapor diffusion of diethyl ether into a concentrated solution in CH_2Cl_2. The structure determination (Table S1, Figure S1) surprisingly revealed the ether-insoluble, lower R_f material to be the α,*β*- rather than the α,α-isomer previously assigned on the basis of polarity. The α,α-arrangement of the more soluble, higher R_f isomer was also confirmed by an X-ray structural determination of its zinc complex [Zn(α,α-BP)] (Table S1, Figure S2). This complex was prepared by reaction of the free base porphyrin H_2(α,α-BP) with zinc acetate in a methanol/dichloromethane solvent mixture. Single crystals of [Zn(α,α-BP)] suitable for X-ray study were ob-

(40) Bookser, B. C.; Bruice, T. C. *J. Am. Chem. Soc.* **1991**, *113*, 4208.
(41) Young, R.; Chang, C. K. *J. Am. Chem. Soc.* **1985**, *107*, 898.
(42) Sanders, G. M.; van Dijk, M.; van Veldhuizen, A.; van der Plas, H. C. *J. Org. Chem.* **1988**, *53*, 5272.
(43) Osuka, A.; Nagata, T.; Kobayashi, F.; Maruyama, K. *J. Heterocycl. Chem.* **1990**, *27*, 1657.
(44) Gunter, M. J.; Mander, L. N. *J. Org. Chem.* **1981**, *46*, 4792.
(45) Sanders, G. M.; van Dijk, M.; Machiels, B. M.; van Veldhuizen, A. *J. Org. Chem.* **1991**, *56*, 1301.

Scheme 2



tained by layering hexane onto a diethyl ether saturated solution. The structure (Figure S2) demonstrates that zinc is coordinated by a diethyl ether in an axial position with a Zn−O distance of 2.20 Å. X-ray structure determinations carried out for H_2(α,α-BP) and [Zn(α,*β*-BP)] also clearly revealed the orientations of two bromomethyl groups, but the quality of the data sets prohibited satisfactory refinements.

Conversion of the Bromomethylporphyrin to the Aminomethylporphyrin. A classical Gabriel synthesis[46,47] was employed to convert the brominated porphyrins H_2(α,α-BP) and H_2(α,*β*-BP) to their corresponding amino derivatives, 5,15-bis(α-amino-*o*-tolyl)-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin H_2(α,α-AP) and H_2(α,*β*-AP), via the imidoporphyrin intermediates 5,15-bis(α-N-phthalimido-*o*-tolyl)-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin, H_2(α,α-IP) and H_2(α,*β*-IP), as shown in Scheme 2. H_2(BP) was allowed to react with potassium phthalimide in anhydrous DMF to form the imidoporphyrin H_2(IP) by nucleophilic substitution. Excess potassium phthalimide was used to drive the reaction to completion. Otherwise, a significant amount of monosubstituted compound was obtained. Exclusion of water from the reaction mixture by using anhydrous DMF and well-dried reactants was critical for the successful transformation. In the presence of water, the benzyl bromide hydrolyzes to benzyl alcohol. The reaction was carried out at a modest temperature (80 °C) since higher temperatures led to significant isomerization. Hydrazinolysis of the imidoporphyrin H_2(IP) was achieved with 98% hydrazine in THF at room temperature, followed by acidic decomposition of the intermediate adducts.[48] The corresponding aminoporphyrin H_2(AP) was obtained in good yields.

Coupling of the Aminoporphyrin with Kemp's Triacid Anhydride Chloride. The target ligand isomers 5,15-bis(α-*N*-(Kemp's triacid imido)-*o*-tolyl)-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin, H_4(α,α-PDK) and H_4(α,*β*-PDK), were synthesized by coupling aminoporphyrin H_2(AP) with Kemp's triacid anhydride-chloride. The reaction was performed in anhydrous pyridine in the presence of a catalytic amount of DMAP according to the literature procedure developed for the synthesis of H_2(XDK).[13] The presence of both acidic and basic groups in H_4(PDK) complicated in the workup and purification procedures. Intensive efforts were expended to find proper reaction conditions, workup procedures and purification methods. The effective procedure is presented in the Experimental Section.

Although H_4(α,*β*-PDK) could in its own right be an interesting molecule, its synthesis was investigated as a surrogate for the desired ligand H_4(α,α-PDK) in this project, considering the similarity of their syntheses. The mono zinc complex of H_4(α,*β*-PDK), [ZnH_2(α,*β*-PDK)], was prepared by reaction with zinc acetate. The structure of [ZnH_2(α,*β*-PDK)] determined by X-ray crystallography (Table S1, Figure S3) revealed the zinc to have inserted into the porphyrin ring. The two Kemp's triacid units orient in a manner such that the two carboxylic acids are directed toward the center of the porphyrin unit. This

(46) Gibson, M. S.; Bradshaw, R. W. *Angew. Chem., Int. Ed., Engl.* **1968**, *7*, 919.
(47) Sheehan, J. C.; Bolhofer, W. A. *J. Am. Chem. Soc.* **1950**, *72*, 2786.
(48) Nigh, W. G. *J. Chem. Edu.* **1975**, *52*, 670.

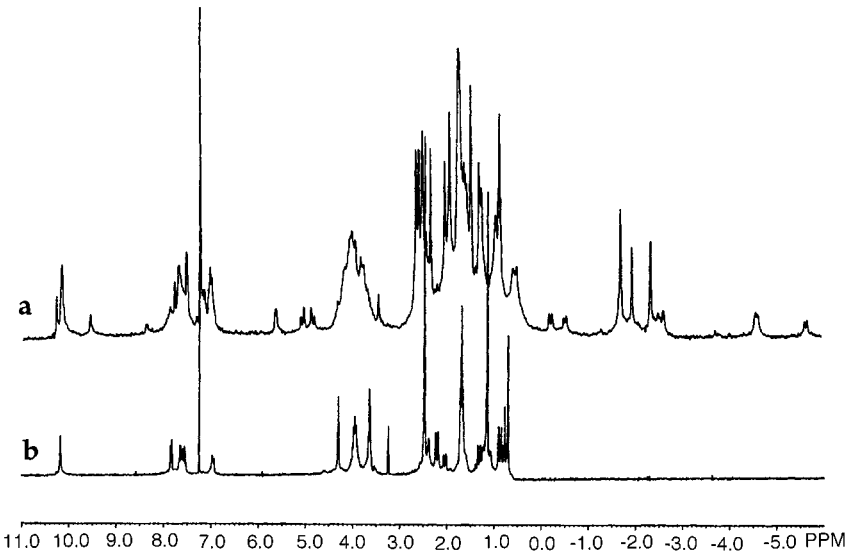


Figure 1. NMR spectra for H_4(α,α-PDK) in $CDCl_3$ (a) before and (b) after addition of a small amount of CD_3OD.

feature is essential for the H_4(α,α-PDK) isomeric ligand to form trinuclear metal complexes having a bis(carboxylato) dimetallic unit situated above the metalloporphyrin ring. The Kemp's triacid units in [ZnH_2(α,*β*-PDK)], however, are not located directly above the porphyrin unit (Figure S3). Such a structure differs from that suggested by ^{1}H NMR for solutions of this complex. Compared with H_2(XDK),[13] the Kemp's triacid unit proton resonances in the ^{1}H NMR spectrum of [ZnH_2(α,*β*-PDK)] shift significantly to higher fields. As an example, the two single methyl peaks shift from 1.32 and 1.30 ppm in H_2(XDK)[13] to 1.02 and 0.76 ppm in [ZnH_2(α,*β*-PDK)]. These high field shifts result from the porphyrin ring current, suggesting that the Kemp's triacid units are located above the porphyrin ring. The discrepancy between the X-ray and solution NMR structures is a result of intermolecular hydrogen bonding interactions in the solid state. As shown in the crystal packing diagram (Figure S4), one Kemp's triacid unit of molecule A is oriented toward the zinc center of molecule B through a hydrogen bonding interaction between imido carbonyl and carboxylic acid oxygen atoms. As a result, the Kemp's acid units are forced to bend away from the center of the porphyrin ring.

Unlike H_4(α,*β*-PDK), H_4(α,α-PDK) has a remarkable and complicated solvent-dependent ^{1}H NMR spectral behavior. Whereas the ^{1}H NMR spectrum of H_4(α,α-PDK) in CD_3OD is well understood and consistent with its expected structure, the spectrum in $CDCl_3$ displays a complicated multiple peak pattern in the expected chemical shift range along with peaks in high field region, *δ* (ppm) −0.23 (d), −0.54 (d), −1.72 (s), −1.96 (s), −2.36 (s), −2.52 (m), −4.62 (m), −5.67 (d) (Figure 1). Upon addition of a small amount of CD_3OD, however, the spectrum converts to one identical to that in CD_3OD (Figure 1). This transformation is ascribed to solvent-dependent hydrogen bonding interactions between the two carboxylic acids. In nonpolar solvents such as $CDCl_3$, such hydrogen bonding is favored and brings the two Kemp's acid units right above the porphyrin ring. As a result, the porphyrin distorts from a planar into a ruffled conformation, as indicated by a structure generated from energy minimization by computer modeling (Figure 2). The interaction, however, is disrupted by solvents such as CD_3OD, which are capable of forming hydrogen bonds with the carboxylic acid. The complicated multiple-peak pattern observed in $CDCl_3$ is therefore ascribed to the broken symmetry. Due to strong ring current effects imposed by the porphyrin unit, the resonances of the Kemp's triacid units appeared at high field. A similar NMR phenomenon was also observed for the zinc complex of H_4(α,α-PDK), [ZnH_2(α,α-PDK)]. The existence and interconversion of multiple conformations may be partially responsible for our inability to grow single crystals of H_4(α,α-PDK) and [ZnH_2(α,α-PDK)] suitable for X-ray structural determination. The proposed convergent structure of H_4(α,α-PDK), however, was unambiguously confirmed through X-ray determinations of a variety of trinuclear complexes[49] including the reported triiron(II) [Fe_3(α,α-PDK)(Lut)$(X)_2$(HX)] (X = Br, I) species.[37]

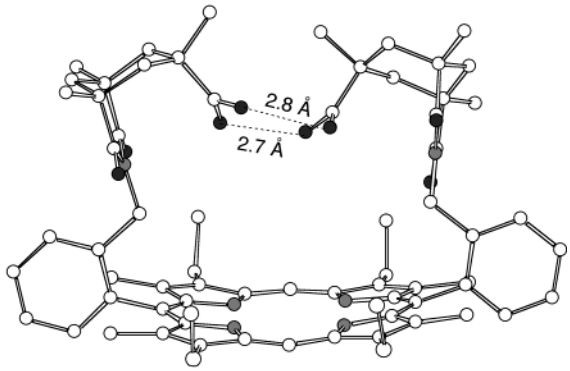


Figure 2. Structure of H_4(α,α-PDK) generated from energy minimization by computer modeling.

Summary and Conclusion

A novel trinuclear ligand system H_4(PDK) was designed and prepared by a multistep synthesis from three basic building blocks, each of which was efficiently synthesized from commercially available materials. A key workup procedure was developed for the controlled reduction of α-bromo-*o*-tolunitrile to form α-bromo-*o*-tolualdehyde in high yield. The intermediate bromoporphyrin was synthesized in good yield, and convenient

(49) Zhang, X.-X.; Lippard, S. J. Unpublished results.

separation procedures of the atropisomers were developed. Continuing isomerization at elevated temperature can be used to increase the yield of a desired isomer. The unambiguous structural determinations of both atropisomers by X-ray crystallography call in to question the validity of commonly used polarity arguments to assign stereochemistry. The structure of [ZnH_2(α,*β*-PDK)] determined by X-ray crystallography differs from that suggested by NMR spectroscopy because of crystal packing. The remarkable and complicated solvent-dependent ^{1}H NMR properties of H_4(α,α-PDK) suggest the existence of hydrogen bonding interactions between two convergent, tethered Kemp's triacid units, as supported in a computer modeling study. This essential feature makes H_4(α,α-PDK) well suited to form trinuclear metal complexes having a bis(carboxylato) dimetallic unit situated above the metalloporphyrin base. By following the procedure described in this report, several grams of H_4(α,α-PDK) can be isolated in ca. 17% overall yield in a period of 2 weeks.

Experimental Section

General Procedures and Methods. Solvents were dried and distilled under nitrogen by standard procedures.[50] Unless otherwise noted, reagents were obtained from commercial suppliers and used as received. All manipulations and reactions were carried out under an inert atmosphere in a Vacuum Atmospheres glovebox or by using standard Schlenk techniques. ^{1}H NMR spectra were recorded on a Bruker AC-250 MHz spectrometer. All spectra were referenced using the residual solvent peak as an internal standard (methanol-d_4, δ = 4.87; chloroform-d_1, δ = 7.24). UV−vis spectra were recorded with a Varian Cary 1E spectrophotometer. FTIR spectra in the range 4000−400 cm^{-1} were obtained and manipulated by using a Bio-Rad SPC3200 FTIR instrument, or a Bio-Rad FTS 135 spectrometer. Samples were prepared as either KBr pellets or Nujol mulls or studied in neat forms. Fast atom bombardment (FAB) mass spectroscopy was performed in the MIT Department of Chemistry Instrumentation Facility with the use of *m*-nitrobenzyl alcohol as the matrix and a parallel run of cesium rubidium iodide for the reference.

α-Bromo-*o*-tolualdehyde. After being purged with argon for 30 min, a solution of α-bromo-*o*-tolunitrile (5.0 g, 25.5 mmol) in dried CH_2Cl_2 (75 mL) was cooled in an ice−water bath and maintained under an argon atmosphere. A solution of diisobutyl aluminum hydride (DIBAL-H, 1.0 M, 26.0 mL, 26.0 mmol) in heptane was added in a dropwise manner over a period of 30 min. The resulting solution was then allowed to warm slowly to room temperature with stirring in a period of 3 h by removing the ice−water bath. The resulting reaction mixture was cooled again with an ice-bath, and then directly poured into a 1000 mL beaker containing ice (100 g) and a precooled HBr aqueous solution (6.0 N, 100 mL). The resulting mixture was vigorously stirred for 1 h without darkening, and then extracted with CH_2Cl_2 three times (100 mL twice; 50 mL once). The CH_2Cl_2 solutions were combined and washed with 1 N $NaHCO_3$ (once) and H_2O (twice), and then dried over anhydrous Na_2SO_4. Evaporation of solvent afforded α-bromo-*o*-tolualdehyde (4.9 g, 97% yield) as a clear brown liquid with high purity. Further purification can be carried out by flash column chromatography (silica gel, CH_2Cl_2): ^{1}H NMR ($CDCl_3$), δ (ppm): 10.21 (s, 1H, CHO), 7.80 (dd, 1H, $^3J_{H-H}$ = 7.2 Hz, $^4J_{H-H}$ = 1.7 Hz, phenyl), 7.54 (td, 1H, $^3J_{H-H}$ = 7.2 Hz, $^4J_{H-H}$ = 1.7 Hz, phenyl), 7.47 (td, 1H, $^3J_{H-H}$ = 7.2 Hz, $^4J_{H-H}$ = 1.7 Hz, phenyl), 7.44 (dd, 1H, $^3J_{H-H}$ = 7.2 Hz, $^4J_{H-H}$ = 1.7 Hz, phenyl), 4.91 (s, 2H, −CH_2Br); IR (neat) υ_{CO} 1700 cm^{-1}; HRMS-EI (M^+) calcd for C_8H_7BrO 197.96803, found 197.96795.

(50) Perrin, D. D.; Perrin, D. R.; Armarego, W. L. *Purification of Laboratory Chemicals*; Pergamon Press: Oxford, 1980.

(3,3′-Diethyl-4,4′-dimethyl-2,2′-dipyrrolyl)methane. The preparation of (3,3′-diethyl-4,4′-dimethyl-2,2′-dipyrrolyl)methane was accomplished from commercially available [5,5′-bis(ethoxycarbonyl)-3,3′-diethyl-4,4′-dimethyl-2,2′-dipyrrolyl]methane through hydrolysis and decarboxylation in the presence of KOH in 95% ethanol under a refluxing Ar atmosphere.[41,42] It was obtained as a light tan crystalline material in 94% yield: ^{1}H NMR ($CDCl_3$), δ (ppm) 7.26 (br s, 2H, NH), 6.35 (m, 2H, 5-H), 3.79 (s, 2H, −CH_2−), 2.47 (q, 4H, −CH_2CH$_3$), 2.03 (s, 6H, −CH_3), 1.12 (t, 6H, −CH_2CH_3).

***cis,cis*-1,3,5-Trimethylcyclohexane-1,3-anhydride-5-Acid Chloride (Kemp's Triacid Anhydride-Chloride).** Kemp's triacid anhydride-chloride was formed from the reaction of Kemp's triacid with $SOCl_2$ by following the literature procedure.[9,10,13]

5,15-Bis(α-bromo-*o*-tolyl)-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin, H_2(BP). Two methods were used for the synthesis of bromoporphyrin H_2(BP). In method A,[43] the porphyrin was prepared by a one-pot method without isolation of the cyclized intermediate porphyrinogen. In method B,[41,44] the porphyrin was synthesized in two steps with the isolation of the intermediate porphyrinogen.

Method A. α-Bromo-*o*-tolualdehyde (246 mg, 1.24 mmol) and (3,3′-diethyl-4,4′-dimethyl-2,2′-dipyrrolyl)methane (185 mg, 1.24 mmol) were dissolved in anhydrous acetonitrile (20 mL). The resulting solution was kept in the dark, by wrapping the flask with an aluminum foil, and maintained under an argon atmosphere. Trichloroacetic acid (35 mg, 0.21 mmol) was added. The reaction mixture was stirred at room temperature for 5 h. A solution of *p*-chloranil (500 mg, 2.0 mmol) in THF (20 mL) was added. The mixture was stirred at room temperature for another 6.5 h. Removal of the solvent gave a residue. The raw material was purified by flash column chromatography (silica gel, CH_2Cl_2) to afford bromoporphyrin H_2(BP) (227 mg, 45% yield) as a mixture of α,α- and α,*β*-atropisomers (H_2(α,α-BP) and H_2(α,*β*-BP)) in a ratio of 35 to 65.

Method B. α-Bromo-*o*-tolualdehyde (1.35 g, 6.77 mmol) and (3,3′-diethyl-4,4′-dimethyl-2,2′-dipyrrolyl)methane (1.56 g, 6.77 mmol) were dissolved in methanol (80 mL). The solution was deoxygenated by bubbling with argon for 30 min. *p*-Toluenesulfonic acid monohydrate (0.36 g, 1.9 mmol) was added. After stirring for 15 min under argon, the mixture was allowed to stand in the dark first at room temperature for 6 h and then at 4 °C for 16 h. The resulting yellow precipitate was collected by filtration and washed with cold methanol to give the crude porphyrinogen. This material (1.2 g, 1.46 mmol) was dissolved in dry THF (100 mL) and then treated with a solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 1.5 g, 6.61 mmol) in dry THF (20 mL). The resulting dark suspension was stirred at room temperature for 3 h. After the solvent was removed by rotary evaporation, the solid residue was treated with 10% aqueous NaOH solution to dissolve the hydroquinone. The remaining precipitates were collected by filtration and washed thoroughly with water. The solid was then dissolved in CH_2Cl_2 and washed once with 1 N $NaHCO_3$ and twice with water. The organic layer was dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a purple solid which was purified by flash column chromatography (silica gel, CH_2Cl_2) to afford bromoporphyrin H_2(BP) (1.0 g, 36% yield) as a mixture of α,α- and α,*β*-atropisomers (H_2(α,α-BP) and H_2(α,*β*-BP) in a ratio of 45 to 55.

Separation of Atropisomers. The mixture of the isomers was separated by flash column chromatography (silica gel, ethyl acetate and/hexane (v/v) = 1/1). The α,α-isomer H_2(α,α-BP) eluted first, followed by the α,*β*-isomer H_2(α,*β*-BP) with CH_2Cl_2 as eluting solvent. Alternatively, the mixture of isomers was treated with diethyl ether and separated by filtration. The undissolved solid was identified as the α,*β*-isomer H_2(α,*β*-BP). The filtrate was concentrated to give the α,α-isomer H_2(α,α-BP). H_2(α,α-BP): ^{1}H NMR ($CDCl_3$), δ (ppm) 10.25 (s, 2H, methine), 8.14 (dd, 2H, $^3J_{H-H}$ = 7.3 Hz, $^4J_{H-H}$ = 1.3 Hz, phenyl), 7.94 (dd, 2H, $^3J_{H-H}$ = 7.3 Hz, $^4J_{H-H}$ = 1.3 Hz, phenyl), 7.84 (td, 2H, $^3J_{H-H}$ = 7.3 Hz, $^4J_{H-H}$ = 1.3 Hz, phenyl), 7.72 (td, 2H, $^3J_{H-H}$ = 7.3 Hz, $^4J_{H-H}$ = 1.3 Hz, phenyl), 4.10 (s, 4H, −CH_2Br), 4.03 (q, 8H, $^3J_{H-H}$ = 7.5 Hz, −CH_2CH$_3$), 2.49 (s,

12H, $-CH_3$), 1.77 (t, 12H, $^3J_{H-H}$ = 7.5 Hz, $-CH_2CH_3$), −2.37 (br s, 2H, −NH); UV−vis (CH_2Cl_2), λ_{max} (nm) 626, 575, 542, 507, 409; HRMS-FAB (M^+) calcd for $C_{46}H_{48}Br_2N_4$ 814.22457, found 814.22360. H_2(α,*β*-BP): ^{1}H NMR ($CDCl_3$) δ (ppm) 10.22 (s, 2H, methine), 8.02 (dd, 2H, $^3J_{H-H}$ = 7.2 Hz, $^4J_{H-H}$ = 1.2 Hz, phenyl), 7.95 (dd, 2H, $^3J_{H-H}$ = 7.2 Hz, $^4J_{H-H}$ = 1.2 Hz, phenyl), 7.83 (td, 2H, $^3J_{H-H}$ = 7.2 Hz, $^4J_{H-H}$ = 1.2 Hz, phenyl), 7.67 (td, 2H, $^3J_{H-H}$ = 7.2 Hz, $^4J_{H-H}$ = 1.2 Hz, phenyl), 4.20 (s, 4H, $-CH_2Br$), 4.00 (q, 8H, $^3J_{H-H}$ = 7.5 Hz, -CH_2CH_3), 2.47 (s, 12H, $-CH_3$), 1.75 (t, 12H, $^3J_{H-H}$ = 7.5 Hz, $-CH_2CH_3$), −2.36 (br s, 2H, −NH); UV−vis (CH_2Cl_2), λ_{max} (nm) 626, 574, 541, 507, 409.

α,α-[5,15-Bis(α-bromo-*o*-tolyl)-2,8,12,18-tetraethyl-3,7,13,17-tetramethyl porphyrin]zinc(II), [Zn(α,α-BP)]. A saturated solution of zinc acetate dihydrate, $Zn(OAc)_2{\cdot}2H_2O$, (54 mg, 0.25 mmol), in methanol was added to a solution of α,α-bromoporphyrin H_2(α,α-BP) (20 mg, 0.025 mmol) in CH_2Cl_2 (5.0 mL). The resulting mixture was stirred in the dark at room temperature. The reaction was monitored by TLC using CH_2Cl_2 as a developing solvent. After 3 h, the solvents were removed and the residue was extracted with $CHCl_3$. The $CHCl_3$ solution was washed once with 1N $NaHCO_3$ and twice with water. After the organic layer was dried over anhydrous Na_2SO_4, the solvent was evaporated to give a pink-purple solid which was purified by flash column chromatography (silica gel, CH_2Cl_2) to afford [Zn(α,α-BP)] (17 mg, 80% yield): ^{1}H NMR ($CDCl_3$), δ (ppm) 10.18 (s, 2H, methine), 8.15 (dd, 2H, $^3J_{H-H}$ = 7.4 Hz, $^4J_{H-H}$ = 1.4 Hz, phenyl), 7.92 (dd, 2H, $^3J_{H-H}$ = 7.4 Hz, $^4J_{H-H}$ = 1.4 Hz, phenyl), 7.83 (td, 2H, $^3J_{H-H}$ = 7.4 Hz, $^4J_{H-H}$ = 1.4 Hz, phenyl), 7.71 (td, 2H, $^3J_{H-H}$ = 7.4 Hz, $^4J_{H-H}$ = 1.4 Hz, phenyl), 4.01 (s, 4H, $-CH_2Br$), 3.99 (q, 8H, $^3J_{H-H}$ = 7.5 Hz, -CH_2CH_3), 2.44 (s, 12H, $-CH_3$), 1.75 (t, 12H, $^3J_{H-H}$ = 7.5 Hz, $-CH_2CH_3$); UV−vis (CH_2Cl_2), λ_{max} (nm) 575, 538, 411.

α,*β*-[5,15-Bis(α-bromo-*o*-tolyl)-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin]zinc(II), [Zn(α,*β*-BP)]. The zinc complex of α,*β*-bromoporphyrin [Zn(α,*β*-BP)] was prepared from the reaction of α,*β*-bromoporphyrin H_2(α,*β*-BP) with zinc acetate dihydrate by a procedure analogous to that given for zinc complex of the α,α-bromoporphyrin [Zn(α,α-BP)]: ^{1}H NMR ($CDCl_3$), δ (ppm) 10.17 (s, 2H, methine), 8.04 (dd, 2H, $^3J_{H-H}$ = 7.6 Hz, $^4J_{H-H}$ = 1.3 Hz, phenyl), 7.95 (dd, 2H, $^3J_{H-H}$ = 7.6 Hz, $^4J_{H-H}$ = 1.3 Hz, phenyl), 7.83 (td, 2H, $^3J_{H-H}$ = 7.6 Hz, $^4J_{H-H}$ = 1.3 Hz, phenyl), 7.68 (td, 2H, $^3J_{H-H}$ = 7.6 Hz, $^4J_{H-H}$ = 1.3 Hz, phenyl), 4.14 (s, 4H, $-CH_2Br$), 3.99 (q, 8H, $^3J_{H-H}$ = 7.5 Hz, -CH_2CH_3), 2.43 (s, 12H, $-CH_3$), 1.75 (t, 12H, $^3J_{H-H}$ = 7.5 Hz, $-CH_2CH_3$); UV−vis (CH_2Cl_2), λ_{max} (nm) 575, 538, 411.

Conversion of H_2(α,*β*-BP) to H_2(α,α-BP) by Thermal Isomerization. A portion of H_2(α,*β*-BP) (385 mg) was dissolved in a mixture of $CHCl_3$ (50 mL) and xylenes (100 mL).[44] The solution was distilled under a stream of Ar until the liquid temperature reached 137 °C. The distillation head was then replaced by a reflux condenser, and the solution was heated to reflux under Ar and protected from light for 35 h. After the solvent was removed by rotary evaporation, the residue was dissolved in a minimum amount of CH_2Cl_2 and layered with Et_2O to effect the precipitation of H_2(α,*β*-BP). The precipitate collected by filtration was mainly H_2(α,*β*-BP), which can be further converted to H_2(α,α-BP) by repeating the above procedure. The filtrate was concentrated and was further purified by flash column chromatography to give pure H_2(α,α-BP) (170 mg).

α,α-5,15-Bis(α-N-phthalimido-*o*-tolyl)-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin, H_2(α,α-IP). Portions of H_2(α,α-BP) (413 mg, 0.51 mmol) and potassium phthalimide (446 mg, 2.44 mmol) were dissolved in anhydrous DMF (50 mL). The resulting solution was heated under argon at 80 °C for 16 h. DMF was removed, and the residue was dissolved in $CHCl_3$ and washed once with 1N $NaHCO_3$ and three times with water. After the organic layer was dried over anhydrous Na_2SO_4 and concentrated in a vacuum, the residue was purified by flash column chromatography (silica gel, ethyl acetate/hexane (v/v) = 1/2) to afford α,α-imidoporphyrin H_2(α,α-IP) (400 mg, 83% yield): ^{1}H NMR ($CDCl_3$), δ (ppm) 10.14 (s, 2H, methine), 8.02−7.33 (m, 16H, phenyl), 4.53 (s, 4H, $-CH_2N<$), 3.98 (q, 8H, $^3J_{H-H}$ = 7.5 Hz, -CH_2CH_3), 2.53 (s, 12H, $-CH_3$), 1.77 (t, 12H, $^3J_{H-H}$ = 7.5 Hz, $-CH_2CH_3$), −2.43 (br s, 2H, −NH); UV−vis (CH_2Cl_2), λ_{max} (nm) 628, 575, 543, 508, 409; HRMS-FAB (M^+) calcd for $C_{62}H_{56}N_6O_4$ 948.43631, found 948.43661.

α,*β*-5,15-Bis(α-*N*-phthalimido-*o*-tolyl)-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin, H_2(α,*β*-IP). The α,*β*-imidoporphyrin H_2(α,*β*-IP) was prepared from the reaction of α,*β*-bromoporphyrin H_2(α,*β*-BP) with potassium phthalimide by a procedure analogous to that given for α,α-imidoporphyrin H_2(α,α-IP): ^{1}H NMR ($CDCl_3$), δ (ppm) 10.17 (s, 2H, methine), 8.05−7.34 (m, 16H, phenyl), 4.55 (s, 4H, $-CH_2N<$), 3.99 (q, 8H, $^3J_{H-H}$ = 7.5 Hz, $-CH_2CH_3$), 2.54 (s, 12H, $-CH_3$), 1.78 (t, 12H, $^3J_{H-H}$ = 7.5 Hz, $-CH_2CH_3$), −2.42 (br s, 2H, −NH); UV−vis (CH_2Cl_2), λ_{max} (nm) 628, 575, 543, 508, 409.

α,α-5,15-Bis(α-amino-*o*-tolyl)-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin, H_2(α,α-AP). An excess amount of 98% hydrazine (1 mL) was added to a solution of α,α-imidoporphyrin H_2(α,α-IP) (220 mg, 0.23 mmol) in THF (20 mL). The resulting mixture was stirred at room temperature in the dark for 17 h. The solvent and excess hydrazine were removed in a vacuum. The residue was treated with 6 N HCl aqueous solution (40 mL) and heated to reflux at 95 °C for 1 h. The precipitates formed were removed by filtration and the filtrate, cooled in an ice−water bath, was made alkaline with concentrated aqueous NaOH solution until a precipitate formed. The aqueous suspension was then extracted with $CHCl_3$ and washed three times with brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in a vacuum to afford α,α-aminoporphyrin H_2(α,α-AP) (140 mg, 88% yield): ^{1}H NMR ($CDCl_3$), δ (ppm) 10.24 (s, 2H, methine), 8.05 (d, 2H, $^3J_{H-H}$ = 7.3 Hz, phenyl), 7.85 (d, 2H, $^3J_{H-H}$ = 7.3 Hz, phenyl), 7.82 (t, 2H, $^3J_{H-H}$ = 7.3 Hz, phenyl), 7.69 (t, 2H, $^3J_{H-H}$ = 7.3 Hz, phenyl), 4.02 (q, 8H, $^3J_{H-H}$ = 7.5 Hz, -CH_2CH_3), 3.45 (br s, 4H, $-CH_2NH_2$), 2.47 (s, 12H, $-CH_3$), 1.77 (t, 12H, $^3J_{H-H}$ = 7.5 Hz, $-CH_2CH_3$), 1.20 (br s, 4H, $-CH_2NH_2$), −2.36 (br s, 2H, −NH); UV−vis (CH_2Cl_2), λ_{max} (nm) 654, 627, 575, 542, 507, 409; HRMS-FAB (M^+) calcd for $C_{46}H_{52}N_6$ 688.42535, found 688.42561.

α,*β*-5,15-Bis(α-amino-*o*-tolyl)-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin, H_2(α,*β*-AP). The α,*β*-aminoporphyrin H_2(α,*β*-AP) was prepared from the reaction of α,*β*-imidoporphyrin H_2(α,*β*-IP) and 98% hydrazine by the same procedure given for α,α-aminoporphyrin H_2(α,α-AP): ^{1}H NMR ($CDCl_3$), δ (ppm) 10.22 (s, 2H, methine), 7.96 (d, 2H, $^3J_{H-H}$ = 7.3 Hz, phenyl), 7.84 (d, 2H, $^3J_{H-H}$ = 7.3 Hz, phenyl), 7.78 (t, 2H, $^3J_{H-H}$ = 7.3 Hz, phenyl), 7.65 (t, 2H, $^3J_{H-H}$ = 7.3 Hz, phenyl), 4.01 (q, 8H, $^3J_{H-H}$ = 7.5 Hz, $-CH_2CH_3$), 3.52 (br s, 4H, $-CH_2NH_2$), 2.46 (s, 12H, $-CH_3$), 1.76 (t, 12H, $^3J_{H-H}$ = 7.5 Hz, $-CH_2CH_3$), 1.21 (br s, 4H, $-CH_2NH_2$), −2.37 (br s, 2H, −NH); UV−vis (CH_2Cl_2), λ_{max} (nm) 654, 627, 575, 542, 507, 409.

α,α-5,15-Bis(α-*N*-(Kemp's triacid imido)-*o*-tolyl)-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin, H_4(α,α-PDK). In a 100 mL three-neck flask equipped with a condenser, H_2(α,α-AP) (441 mg, 0.640 mmol), Kemp's triacid anhydride chloride (331.2 mg, 1.280 mmol), 2,6-di-*tert*-butyl pyridine (612 mg, 3.20 mmol) and DMAP (7.82 mg, 0.064 mmol) were dissolved in anhydrous toluene (20 mL). After it was purged with Ar for 30 min, the reaction solution was heated at 90 °C with protection from light for 18 h. The reaction mixture was cooled to room temperature, treated with $CHCl_3$ (50 mL), and washed with HCl solution (100 mL, 1.2 N). The water phase was extracted further twice with $CHCl_3$ until the $CHCl_3$ phase was colorless. The combined greenish $CHCl_3$ extracts were washed three times with water until the color changed to red purple and the aqueous phase was neutral (pH ∼ 6−7). After drying over anhydrous Na_2SO_4, the organic layer was concentrated and subjected to flash column chromatography (silica gel, THF) to afford purple H_4(α,α-PDK) (585 mg, 81%): ^{1}H NMR (250 MHz, CD_3OD, 296 K), δ (ppm) porphyrin unit: 10.26 (s, 2H, methine), 7.78 (d, 2H, $^3J_{H-H}$ = 7.2 Hz, phenyl), 7.75 (pseudo-t, 2H, $^3J_{H-H}$ = 7.45 Hz, $^3J_{H-H}$ = 7.6 Hz, phenyl), 7.62 (pseudo-t, 2H, $^3J_{H-H}$ = 7.2 Hz, $^3J_{H-H}$ = 7.45 Hz, phenyl), 7.19 (d, 2H, $^3J_{H-H}$ = 7.6 Hz, phenyl), 4.49 (s, 4H, $-CH_2N<$), 4.02 (q, 8H, $^3J_{H-H}$ = 7.5 Hz, -CH_2CH_3), 2.53 (s, 12H, $-CH_3$),

1.78 (t, 12H, $^3J_{H-H}$ = 7.5 Hz, $-CH_2CH_3$), Kemp's triacid unit: 2.15 (d, 4H, $^2J_{H-H}$ = 14.0 Hz, cyclohexyl-H), 1.96 (d, 2H, $^2J_{H-H}$ = 13.0 Hz, cyclohexyl-H), 1.31 (d, 2H, $^2J_{H-H}$ = 13.0 Hz, cyclohexyl-H), 0.89 (d, 4H, $^2J_{H-H}$ = 14.0 Hz, cyclohexyl-H), 1.02 (s, 12H, $-CH_3$), 0.75 (s, 6H, $-CH_3$); ^{1}H NMR ($CDCl_3$), very complicated peaks in the range between 11 and 0 ppm plus high field peaks, δ (ppm) −0.23 (d), −0.54 (d), −1.72 (s), −1.96 (s), −2.36 (s), −2.52 (m), −4.62 (m), −5.67 (d); UV−vis ($CHCl_3$), λ_{max} (nm) 651, 622, 574, 543, 509, 435(s), 409; UV−vis ($CHCl_3$ + CH_3OH), λ_{max} (nm) 651, 623, 572, 541, 509, 408; FTIR (KBr, cm^{-1}) 3441, 2963, 2930, 2872, 1730, 1684, 1462, 1377, 1329, 1261, 1166, 1091, 1059, 1001, 971, 953, 943, 844, 754, 685; HRMS-FAB (M^+) calcd for $C_{70}H_{80}N_6O_8$ 1132.60376, found 1132.60442.

α,β-5,15-Bis(α-*N*-(Kemp's triacid imido)-*o*-tolyl)-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin, H_4(α,β-PDK). Portions of H_2(α,β-AP) (113 mg, 0.16 mmol), Kemp's triacid anhydride-chloride (85 mg, 0.32 mmol) and DMAP (4 mg, 0.032 mmol) were dissolved in anhydrous pyridine (10 mL). The resulting solution was heated under argon at 95 °C for 16 h. After the pyridine was removed by rotary evaporation, the residue was dissolved in $CHCl_3$ and washed three times with brine. After the organic layer was dried over anhydrous Na_2SO_4 and concentrated in a vacuum, the residue was purified by flash column chromatography (silica gel, ethyl acetate/methanol (v/v) = 10/1) to afford H_4(α,β-PDK) (167 mg, 90%): ^{1}H NMR (250 MHz, $CDCl_3$, 296 K), δ (ppm) porphyrin unit: 10.16 (s, 2H, methine), 8.00−6.98 (m, 8H, phenyl), 4.23 (s, 4H, $-CH_2N<$), 3.92 (q, 8H, $^3J_{H-H}$ = 7.5 Hz, $-CH_2CH_3$), 2.49 (s, 12H, $-CH_3$), 1.71 (t, 12H, $^3J_{H-H}$ = 7.5 Hz, $-CH_2CH_3$), Kemp's triacid unit: 0.83 (br s, 12H, $-CH_3$), 0.41 (br s, 12H, $-CH_3$), cyclohexyl proton was not identified due to the low quality of the spectra, see ^{1}H NMR of [ZnH_2(α,β-PDK)]; UV−vis (CH_2Cl_2), λ_{max} (nm) 653, 626, 574, 542, 508, 408; HRMS-FAB (M^+) calcd for $C_{70}H_{80}N_6O_8$ 1132.60376, found 1132.60329.

α,α-[5,15-Bis(α-*N*-(Kemp's triacid imido)-*o*-tolyl)-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin]zinc-(II), [ZnH_2(α,α-PDK)]. To a purple solution of H_4(α,α-PDK) (146 mg, 0.13 mmol) in $CHCl_3$ (10 mL) was added a solution of $Zn(OAc)_2 \cdot 2H_2O$ (285 mg, 1.30 mmol) in CH_3OH (5 mL). The resulting pink purple solution was stirred at room temperature for 13 h. After the solvents were removed, the residue was treated with a small amount of CH_2Cl_2 and filtered through Celite. The filtrate was concentrated and purified by flash column chromatography (silica gel, ethyl acetate) to afford [ZnH_2(α,α-PDK)] as a pink purple solid (115 mg, 75%): UV−vis (CH_2Cl_2), λ_{max} (nm) 576, 544, 417; FTIR (KBr, cm^{-1}) 3447, 2964, 2931, 2872, 1734, 1701, 1680, 1593, 1454, 1411, 1377, 1334, 1267, 1232, 1167, 1106, 1088, 1059, 1001, 872, 951, 878, 821, 758, 709, 669, 624, 598, 475; HRMS-FAB (M^+) calcd for $C_{70}H_{78}N_6O_8Zn$ 1194.51726, found 1194.51619.

α,β-[5,15-Bis(α-*N*-(Kemp's triacid imido)-*o*-tolyl)-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin]-zinc(II) [ZnH_2(α,β-PDK)]. A saturated solution of zinc acetate dihydrate (43 mg, 0.20 mmol) in methanol was added to a solution of H_4(α,β-PDK) (15 mg, 0.013 mmol) in CH_2Cl_2 (4 mL). The resulting mixture was stirred in the dark at room temperature. The reaction was monitored by TLC using CH_2Cl_2 as the developing solvent. After 6 h, the solvents were removed and the residue was extracted with $CHCl_3$ and washed with water. After the organic layer was dried over anhydrous Na_2SO_4, the solvent was evaporated to give a pink-purple solid which was purified by flash column chromatography (silica gel, ethyl acetate) to afford [ZnH_2(α,β-PDK)] (13 mg, 85%). Recrystallization from vapor diffusion of pentane into a concentrated solution of [ZnH_2(α,β-PDK)] in ethyl acetate at room temperature in a period of two weeks afforded single crystals which appeared suitable for X-ray crystallography: ^{1}H NMR (250 MHz, CD_3OD, 296 K), δ (ppm) porphyrin unit: 10.09 (s, 2H, methine), 7.81 (d, 2H, $^3J_{H-H}$ = 7.2 Hz, phenyl), 7.71 (pseudo-t, 2H, $^3J_{H-H}$ = 7.45 Hz, $^3J_{H-H}$ = 7.6 Hz, phenyl), 7.60 (pseudo-t, 2H, $^3J_{H-H}$ = 7.2 Hz, $^3J_{H-H}$ = 7.45 Hz, phenyl), 7.21 (d, 2H, $^3J_{H-H}$ = 7.6 Hz, phenyl), 4.51 (s, 4H, $-CH_2N<$), 4.00 (q, 8H, $^3J_{H-H}$ = 7.5 Hz, $-CH_2CH_3$), 2.46 (s, 12H, $-CH_3$), 1.76(t, 12H, $^3J_{H-H}$ = 7.5 Hz, $-CH_2CH_3$), Kemp's triacid unit: 2.16 (d, 4H, $^2J_{H-H}$ = 14.0 Hz, cyclohexyl-H), 2.05 (d, 2H, $^2J_{H-H}$ = 13.0 Hz, cyclohexyl-H), 1.38 (d, 2H, $^2J_{H-H}$ = 13.0 Hz, cyclohexyl-H), 0.99 (d, 4H, $^2J_{H-H}$ = 14.0 Hz, cyclohexyl-H), 1.02 (s, 12H, $-CH_3$), 0.76 (s, 6H, $-CH_3$); UV−vis (CH_2Cl_2), λ_{max} (nm) 575, 543, 413.

X-ray Crystallography. X-ray diffraction studies were carried out using a Bruker (formerly Siemens) SMART CCD X-ray instrument with a graphite-monochromatized Mo Kα radiation (λ = 0.710 73 Å) controlled by a Pentium-based PC running the SMART software package,[51] as previously described.[52] Crystals were mounted at room temperature on the ends of quartz fibers in Paratone N. Data collection was carried out at −85 °C maintained by a Siemens LT-2A nitrogen cryostat. Crystals were judged to be of acceptable quality on the basis of initial unit cell matrixes and reflection profiles. The raw data frames were integrated by the SAINT software package[53] on a Silicon Graphics Indy workstation. The refinements were carried out with the SHELXTL software package.[54] Hydrogen atoms were placed at calculated positions (C−H = 0.95−1.00 Å), with thermal parameters set equal to 1.2 times (1.5 times for methyl groups) B_{eq} of the atom to which they were bound. They were included, but not refined, in the final least-squares cycles. Crystallographic information is summarized in Table S1 (Supporting Information).

Computer Modeling. The molecular mechanics optimized structure of H_4(α,α-PDK) was obtained by CAChe program using MM2 force field parameters. The energy terms included in calculation are bond stretch, bond angle, dihedral angle, improper torsion, van der Waals, electrostatics, and hydrogen bond.

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Supporting Information Available: X-ray crystallographic information including ORTEP and crystal packing diagrams (Figures S1−S4). This material is available free of charge via the Internet at http://pubs.acs.org.

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(51) *SMART. 4.0: Bruker Analytical X-ray System*; Madison, WI., 1994.
(52) Feig, A. L.; Bautista, M. T.; Lippard, S. J. *Inorg. Chem.* **1996**, *35*, 6892.
(53) *SAINT 4.0: Bruker Analytical X-ray System*; Madison, WI, 1995.
(54) *SHELXTL: Struture Analysis Program 5.1; Bruker Analytical X-ray System*; Madison, WI, 1997.