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Design and Synthesis of Porphyrins Bearing Rigid Hydrogen Bonding Motifs: Highly Versatile Building Blocks for Self-Assembly of Polymers and Discrete Arrays

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Abstract

Two aldehydes, 2,6-diacetamido-4-formylpyridine (**7**) and 1-butyl-6-formyluracil (**11**), are used to synthesize five pyridyl and four uracyl *meso*-substituted porphyrins. With these complementary porphyrin building blocks, it is possible to build various types of multi-porphyrin supramolecules with different spatial relationships in predefined geometries. The formation and properties of self-complementary dimers and a closed tetrameric square are presented as a basis of comparison to the latter system in the solid state. An X-ray structure of 5,10-bis(4-*tert*-butylphenyl)-15,20-bis-(3,5-diacetamido-4-pyridyl)porphyrin confirms its molecular structure and reveals a hydrogen-bonded supramolecular organization mediated by water molecules.

Introduction

Self-assembly into specifically designed structures involves the spontaneous association of molecules through intermolecular interactions. The ability to control the supramolecular organization of molecular entities by noncovalent interactions remains a challenging goal in materials science, because of our still imperfect ability to predictably design supramolecular structures in solution and in the solid state. Due to their key role in many important biological systems, the self-assembly of porphyrin derivatives has attracted considerable attention because of their photoelectric properties, their potential use as components of nanometer scale photonic devices, and as novel functional materials. In addition to the free bases, the functionality (luminescence, redox, electronic, etc.) of these large, rigid aromatic macrocycles may be altered or fine-tuned by formation of various metal derivatives. For these reasons, porphyrins and metallo-porphyrins are particularly attractive molecular species to incorporate into supramolecular assemblies with special built-in properties or functions. Much effort has been applied to the design and synthesis of covalent porphyrinic arrays analogous to those found in nature for charge separation, electron transport, and signal or energy transduction. Formation of multiple hydrogen bonds between complementary molecular components is widely used in the fabrication of

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supramolecular assemblies because of their strength, directionality, specificity, and reversibility. Preparation of monomeric hydrogen bond recognition unit-bearing chromophores allows the self-assembly of both polymers and discrete arrays with various structures in high yields by appropriate combinations of the molecular building blocks.

Designed porphyrin arrays have been formed by hydrogen bonding, axial metallo-porphyrin coordination, and coordination of exocyclic ligands. Several topologically complex structures such as catenanes and rotaxanes have utilized porphyrins. Porphyrins have been incorporated into lipid membranes to form photo transistors and have been used in read-write devices and as receptors. Several recent reviews on self-assembly of various molecules, including porphyrins, put the present work into context. One conclusion that may be drawn from these numerous studies is that the nature of the chemical linker—covalent, coordination, or hydrogen bond—is just as important to the function of the array as the topology of the chromophores. Thus, porphyrinic squares formed by metal ion coordination have substantially different photophysical properties than porphyrin squares formed via hydrogen bonding. For example, if fluorescence is a desired property of the material, say for a ns luminescent switch, then hydrogen bonding is preferred over metal ion coordination or acetylenic linkers, because these later reduce the quantum yield by heavy atom effects and energy or electron transfer, respectively. While there is an ever increasing number of discrete porphyrin arrays mediated by metal ion coordination, there are few discrete arrays mediated by hydrogen bonding.

The primary objective of this work is to develop synthetic strategies for two sets of porphyrin building blocks bearing rigidly linked peripheral complementary triple hydrogen bonding moieties (Figure 1), and the heretofore unknown aldehydes. The issue of a general synthesis of porphyrins bearing complex heterocyclic substituents is yet unresolved, *vide infra*. These can be joined into a variety of discrete nanostructures with remarkable control and precision. By mixing these complementary synthons in organic solvents with accurately controlled stoichiometry, the directed triple hydrogen bonding moiety makes it possible to form various types of rigid multi-porphyrin arrays with different, designed spatial relationships. Low molecular weight polymers with somewhat tunable size, depending on the thermodynamics of binding, and molecular organization into higher order structures are also possible. The use of free base or metalloporphyrin building blocks enables the fabrication of arrays with predetermined metalation states. These building blocks also provide hydrogen-bonded pathways through which energy or electron transfer might be facilitated. In addition, an X-ray study of a 5,15-disubstituted pyridyl derivative reveals an unexpected new mode of hydrogen-bonded supramolecular aggregation mediated by adventitious water molecules.

Results and Discussion

The syntheses of two aldehydes **7** and **11** are shown in Schemes 1 and 2. The direct amination of 4-methylpyridine, **1**, with sodium amide in a tetralin solution affords 2,6-diamino-4-methylpyridine, **2**, in 65% yield. This factor of 2 increase in yield over previous methods is largely due to milder reaction conditions (slowly heating by stages) and workup (hydrolysis with ethanol). 2,6-Diamino-4-methylpyridine, **3**, is made through acylation

of **2** with acetic anhydride. The oxidation of compound **3** with peracetic acid yields 2,6-diacetamido-4-methylpyridine-1-oxide, **4**. Refluxing **4** in acetic anhydride results in the oxidation of the methyl group by a transfer of the intermediate 1-acetoxy group to yield 2-diacetamido-6-acetamido-4-acetoxy methylpyridine **5**. Selective hydrolysis of one acetate of the imide and the ester group of **5** with K_2CO_3 in a methanol/water solution affords the 2,6-diacetamido-4-hydroxymethylpyridine, **6**. The alcohol **6** is oxidized with PCC (on alumina) under ultrasound conditions to yield 2,6-diacetamido-4-formylpyridine, **7**, where yields as high as 65% are observed in small-scale oxidation reactions. Starting from **2**, the 26–32% overall yield of this synthetic route (Scheme 1) is reasonable because of the inexpensive starting materials and the easy scale-up. Other routes to this aldehyde are not successful because of the substantial electronic effects at the 4 position. For example, the 2,6-diamino-3-formylpyridine isomer can be synthesized by the formylation of 2,6-diaminopyridine by a Vilsmeier reaction. Completely optimized structure calculations using Gaussian 98 (B3LYP/6-311**) on aldehyde **7** indicate that both the acetamido and aldehyde groups are coplanar with the pyridine ring, with the amide oxygen atoms pointing toward the ring. These calculations also suggest that there is some hydrogen bonding between the amide oxygen atoms and the pyridyl hydrogens, and one of the pyridyl hydrogens is near enough to hydrogen bond with the aldehyde oxygen. The difference in the chemical shifts for the two pyridyl protons is calculated (GIAO) to be 0.220 ppm in the gas phase, and that measured in chloroform-*d* is <0.07 ppm. Interestingly, the pyridyl protons sense the formation of the self-complementary hydrogen bond dimer of **II**, manifested as a small chemical shift of ~0.1 ppm, which is consistent with the expected inductive and geometric effects, Supporting Information.

The synthesis of the complementary 1-butyl-6-formyl-uracil, **11**, from 6-formyluracil, **8**, is substantially different than that of the known 1-butyl-5-formyluracil^{5a} (Scheme 2). Unlike the 5-formyl derivative, the 6-formyluracil does not alkylate preferentially at the 1-position so must be protected as the acetal, alkylated, and deprotected. Trimethyl orthoformate in methanol/methylene chloride and **8** were refluxed for 10 h in the presence of the *p*-toluenesulfonic acid to form the 6-(dimethoxymethyl)uracil in 86% yield. The dimethyl acetal was alkylated with *n*-butylbromide catalyzed by K_2CO_3 in DMSO at room temperature for 72 h to form the 1-butyl-6-(dimethoxymethyl)uracil (37% based on *n*-butylbromide) and two byproducts. The 1-butyl-6-(dimethoxymethyl)uracil could not be converted to its corresponding aldehyde under a variety of aqueous acid conditions, so a Lewis acid, BBr_3 , in CH_2Cl_2 was used to cleave the dimethyl acetal at -78 °C in 87% yield. In dry solvents the uracil vinyl proton can be observed as two peaks, possibly as a consequence of self-complementary hydrogen bonding of **11**.

Both sets of porphyrin building blocks were prepared by the Adler synthesis (Schemes 3 and 4) and modifications thereof. Using a mixture of two different aldehydes results in a mixture of six porphyrins in yields that are weighted by the reactivity, the solubility, and the relative amounts of the aldehydes. All three of these can be exploited to obtain maximum yields of the desired porphyrins, vide infra. Since the polarities of the six porphyrins are very different, they are readily separated by column chromatography. The mixed aldehyde condensation was chosen for several reasons. (1) Heterocyclic aldehydes and/or those

bearing Lewis bases are generally not tolerated or have poor yields using the Lindsey porphyrin syntheses as well as most of the $[n + (4 - n)]$ coupling reactions. (2) The five compounds containing the heterocycles are all needed as building blocks for the self-assembled arrays. (3) The Adler synthesis and its modifications are quite amenable to large scale, multigram reactions without significant sacrifice in yields or complications in purification. (4) All the porphyrins and isomers can be well characterized by the ^1H NMR spectra in the aromatic region, especially by the pyrrole β -H. Thus, with ample quantities of the two aldehydes in hand, a number of porphyrin syntheses were explored: three different reaction solvents, acetic acid, propionic acid, and a mixture of nitrobenzene/acetic acid were tried each with and without zinc acetate as a possible templating agent. All these conditions give good results with **7**, but **11** was more problematic.

To increase the yield of the four porphyrin building blocks bearing both heterocyclic and alkylphenyl groups, we adopted three measures: (i) increasing the relative amount of the heterocyclic aldehydes, (ii) decreasing the concentration of the reaction mixture (0.05 M), (iii) for the uracyl porphyrin building blocks, changing the reactant addition order whereby the 4-*tert*-butylbenzaldehyde was added 10 min *after* adding the pyrrole rather than adding two aldehydes together. During the course of this investigation only one method for the synthesis of the tetrauracylporphyrin was discovered, namely using acetic acid and nitrobenzene as reaction solvents with zinc acetate (Scheme 4.). The 5.1% yield of **XII** is consistent with previous Adler synthesis considering that it bears a nonaromatic heterocycle with a sterically hindering substituent next to the aldehyde.

The one striking aspect of the physical properties of both the diheterocyclic porphyrin isomers is the abnormally low solubility of the 5,15-isomer compared to that of the 5,10-isomer. In nonpolar organic solvents the solubility of the 5,10-disubstituted porphyrins is usually expected to be less than that of the 5,15-isomers due to greater polarity; however, on the contrary, these 5,10-porphyrins are found to have much greater solubility than the 5,15-isomers. As discussed below, this anomalous solubility is explained by the self-complementary hydrogen-bond self-assembly of linear polymeric tapes vs closed tetrameric squares.

While the characterization of the 3,5-diacetamido-4-pyridylporphyrins is straightforward, the characterization of meso-1-butyl-6-uracylporphyrins merits comment. The four 1-butyl-6-uracyl groups are rigidly linked to the meso-positions of the porphyrin and rotation about the connecting bond is hindered by the butyl substituents. Thus the 1-butyl-6-uracyl group is oriented nearly normal to the porphyrin plane, projecting the butyl substituents above or below the macrocycle. The ^1H NMR spectra, see Supporting Information, of the tetrauracyl compound **XII** reveals that: (1) all the chemical shifts of the butyl group are shifted up field due to ring current effects; (2) the methylene group next to the 1-N atom showed four sets of multiplets rather than one triplet and the methyl group showed four sets of triplets rather than one triplet. This proves that the butyl groups are on the 1-positions of the uracyl, and that there are four rotameric forms in a ratio of 1:3:2:1 from low to high field. The statistical ratio for the $\alpha\alpha\alpha\alpha$, $\alpha\alpha\alpha\beta$, $\alpha\alpha\beta\beta$, and $\alpha\beta\alpha\beta$ rotamers would be 1:4:2:1, respectively (α above and β below the porphyrin plane). The integral areas of the terminal methyl group are consistent with the *N*-methylene, but may be in a different order.

The observed deviations from the ideal ratios may be due to losses during the purification process. The rotameric forms of **VIII-XII** result in self-assembled supramolecular species with different isomeric forms, but the isomers are not observed. There are also no detectable consequences on the energetics and kinetics of the self-assembly process since the uracyl ADA (A = hydrogen bond acceptor, D = hydrogen bond donor) recognition function(s) are directed along the porphyrin plane.

The ^1H NMR spectra of the various other uracyl porphyrin derivatives, **VIII-XI**, are similarly complex due to the presence of both 4-*tert*-butylphenyl and 1-butyl-6-uracyl groups and the resulting rotamers. Each porphyrin face is different in the monouracyl porphyrin, **VIII**. This results in an AB, A'B' system, where A', B' represents the phenyl protons on the opposite side of the macrocycle relative to the butyl group on the uracyl. Thus for **VIII**, the phenyl protons are observed as multiplets rather than a simple AB quartet. This spectrum of **VIII** shows the expected diagnostic pattern in the β -pyrrole region for this type of derivative, where there are four different chemical environments that should result in two AB quartets, but only the quartet from the pyrroles nearest the heterocycle is observed, while those on the opposite side of the heterocycle are observed as a singlet even on the 500 MHz instrument.

For analytical purposes both rotamers of **IX** and **X**, were isolated. Both the 5,15- and 5,10- compounds can exist as $\alpha\alpha$ or $\alpha\beta$ rotamers, each with a different symmetry, with respect to the relative orientation of the two 1-butyl-6-uracyl groups. Thus, the chemical environments of the porphyrin faces are the same for the $\alpha\beta$ rotamers and different for the $\alpha\alpha$ rotamers for both **IX** and **X**. As in the mono substituted derivative, these rotameric forms are readily observed in the ^1H NMR in the region of the two 4-*tert*-butylphenyl groups. A simple doublet of doublets for the phenyl groups of the $\alpha\beta$ rotamers of both compounds is observed, while multiplets for the same groups are observed for the $\alpha\alpha$ rotamers. Because the pyrrole β -H are in the porphyrin plane, the rotameric forms of **IX** and **X** are not observed in this region, so there are the expected four different pyrrole resonances in **X** and two for **IX**.

Structural Studies

As an additional, unexpected example of the intrinsic tendency of these compounds to aggregate by hydrogen bonding, we also present an X-ray study of **IV**. Atom names, displacements from planarity and an edge-on view of the macrocycle are given in Figure 2. The crystallographic determination provides unambiguous identification of **IV**. Complete experimental details, atomic coordinates and molecular geometry are included in the Supporting Information. The C5-, C10-, and C20-meso substituents are completely ordered, but the *tert*-butylphenyl group at C15 exists in two discrete orientations with 75/25% occupancies. (Only the orientation of the major component is shown in Figure 2.)

The skeleton of **IV** is mainly saddled with some degree of ruffling. The C β atoms in each of the four pyrrole rings exhibit substantial unequal displacements from the mean porphyrin plane that range between 0.34 and 0.48 Å (see Figure 2). The deviations of the meso carbons are also unequal; they are smaller at C5 and C10, 0.02 Å and -0.07 Å, than at C15 and C20,

0.17 Å and -0.13 Å. The edge-on view in Figure 2 further illustrates the distorted conformation of the macrocycle, with rings B and D above the mean plane and rings A and C below it. Note that such out-of-plane distortions of the porphyrin macrocycle have been shown to have significant effects on the optical, redox and excited-state properties of the chromophores. Biological systems containing porphyrinic proteins such as those used in photosynthesis and electron transport exploit these effects to fine-tune their reactivity and photophysical properties.

As observed in other saddled porphyrins, the dihedral angles between the meso-substituents and the porphyrin plane are unusually acute. They assume values of 62° at C5, 36° at C10, 60° and 72° at C15, and 62° at C20. The unusual dihedral angle of 36° of the C10 substituent, compared to the nearly perpendicular angles of 80–90° normally observed in planar aryl-substituted porphyrins, is most likely related to its participation in hydrogen bonds (vide infra).

The sample was crystallized from a mixture of ethyl acetate and hexane, but the crystals do not incorporate either of these solvents. Instead, the lattice contains 2.5 molecules of adventitious water per porphyrin. The unexpected water molecules (O5 and O6) mediate a more extensive supramolecular array of **IV** via multiple hydrogen bonds (Figure 3).

For simplicity, the basic porphyrin building blocks of this array are designated as 1, 2, 3, and 4. Only molecule I comprises the crystallographic asymmetric unit; the rest are generated by space group operators. Molecules 1 and 2 are joined by two reciprocal O1...N9 and two reciprocal N5...N10 hydrogen bonds at 3.02 Å and 3.05 Å. This dimeric unit is further incorporated into a complex multi-porphyrin array. O2 of molecule 1 associates with O6 (a water molecule of solvation) with an O2...O6 distance of 2.84 Å. O6 then hydrogen bonds to N6 of molecule 3 which is 2.99 Å from it. N7 of molecule 1 associates with O5 (another water molecule of solvation) with N7...O5 = 3.00 Å. O5 sits 2.82 Å away from O4 of molecule 4. (There are additional interactions involving O7, a third water of crystallization that is present only 50% of the time.)

All five possible hydrogen-bond donors and acceptors (O1, N6, N5, N7, and O2) of the C5-meso substituent participate in the network formation, whereas only N9, N10 and O4 of the C10-meso substituent participate, and may thus contribute to the differences in the orientations of the peripheral rings. The closest approach of pyrrole ring centers (A and D) is 3.87 Å involving 1 and another molecule not involved in the hydrogen bonding with 1. Since the center to center distance of 1 and 2 is 12.70 Å, they interact only at the periphery. The structure reveals that there are no substantial π - π interactions in this arrangement of macrocycles in the solid state. Therefore, the degree of porphyrin distortion caused solely by hydrogen bonding in this single-component system is unprecedented.³¹ These results also indicate that the intentional addition of water to molecules designed to form networks or arrays mediated by hydrogen bonding may well lead to novel aggregates, as evidenced by this structure.

Self-Assembled Squares in Solution.

The preponderance of evidence from ^1H NMR, UV-visible, ESI-MS, light scattering, and osmometry suggests that **IV** self-assembles into tetrameric squares in solvents with low hydrogen-bonding potential by self-complementary hydrogen bonds. This is well demonstrated by fits of the chemical shift of the amide proton versus concentration to yield an apparent equilibrium constant, K , and the number of molecules in the final assembly, n (Figure 4A). If there are several products or dynamic processes, such as the breaking apart of one or more sets of hydrogen bonds occurring on the NMR time scale, these results will only give rough estimates of K , but this serves as a basis of comparison for the square formed by complementary H-bonds, below. Analysis of the NMR data for the self-complementary self-assembly of the square tetramer of **IV** yields $K = 2.1 \pm 1 \times 10^9 \text{ M}^{-3}$, and $n = 3.9 \pm 0.3$ in chloroform. In toluene the equilibrium constants are greater, as expected, where K is $\sim 2 (1 \times 10^{10} \text{ M}^{-3})$. ESI-MS and vapor phase osmometry data also indicate a tetrameric species.

The thermodynamics of these self-complementary systems in solution are discussed herein. The association for the diacetamidopyridyl moiety is usually considered weak,

ΔG ranges from 4 to 13 kJ mol $^{-1}$, and the double hydrogen bond considered the dominant interaction. However, the strengths of these recognition units are substantially altered by the presence of the directly linked porphyrin. Thus there is likely an equilibrium between the various self-complementary interactions of the diacetamidopyridyl groups - double, triple, quadruple hydrogen bonds. Van'tHoff plots of the ^1H NMR data for the self-complementary dimerization of **II** indicate ΔH of the dimer is $\sim 21 \pm 5 \text{ kJ mol}^{-1}$ in toluene versus the expected $\sim 13 \text{ kJ mol}^{-1}$ for the alkyl substituted derivative in the same solvent. AM1 calculations indicate that the presence of a phenyl group on the 4 position of the 2,6-diacetamidopyridyl moiety increases the self-complementary H-bond enthalpy by $\sim 4 \text{ kJ mol}^{-1}$. Typically, the electronic effects of the porphyrin are greater than the phenyl group, so a further increase in the ΔH of the self-complementary interaction(s) is expected and calculated to be $\sim 6 \text{ kJ mol}^{-1}$ greater than the parent recognition unit. Thus the experimental and calculated results are qualitatively consistent. The 90° geometry of the rigidly linked recognition groups on the porphyrins, and the thermodynamic stability of the self-assembled H-bond squares compared to other structures, ensure that the squares are formed in $\sim 75\%$ in chloroform, and $\sim 90\%$ in toluene. Both experimental and computational results show that the presence of the phenyl has little effect on the self-complementary 1-butyl-6-uracil system. Calculations indicated there should be a modest increase of $\sim 3 \text{ kJ mol}^{-1}$ for hetero-complementary 2,6-diacetamido-4-phenylpyridine and 1-butyl-6-phenyluracil. The H-bond strengths between the complementary porphyrins **II**, and **VIII**, are calculated to be 45 kJ mol^{-1} , $\sim 7 \text{ kJ mol}^{-1}$ greater than for the isolated recognition units bearing neither porphyrin nor phenyl substituent. Thus the porphyrin ring is expected and observed to enhance the basicity of the pyridyl nitrogen and therefore the H-bond strength. This is a well-documented phenomenon in the coordination chemistry of pyridylporphyrins.

The formation of a tetrameric square from two equivalents each of **IV** and **X** (Scheme 5) in THF, used because of the limited solubility of **X**, is indicated by similar experiments as described above. The overall shape of the NMR concentration vs amide chemical shift (Figure 4B) clearly indicates a tetrameric species with $n = 4$ and an apparent

equilibrium constant, see caveats vide supra, of $6 = 3 \times 10^{12} \text{ M}^{-3}$ which is somewhat greater than that estimated solely by equilibrium considerations from the C1/2 data. Note that the C1/2 for the complementary square is about 2-fold less than that of the self-complementary species, and the ppm for the amide protons is a factor of 5 greater. These are all indicative that the complementary interactions between the uracyl and diacetamidopyridyl moieties, calculated by various means to be $\sim 45 \text{ k J mol}^{-1}$, are much stronger than either self-complementary interaction even in a solvent known to be less favorable to H-bonding than chloroform. Dynamic light scattering detects only species with $\sim 4 \text{ nm}$ hydrodynamic radius between 0.04 and 0.1 mM. Vapor phase osmometry experiments using concentrations between 0.1 and 1 mM yields an average molecular weight of $3500 \pm 300 \text{ da}$. ESI-MS using a mixture of **IV**, Co(III)**IV**, and **X** (1:1:2) shows the doubly charged tetramer as well as other multimers and the monomers. Taken together, these data indicate that the complementary tetrameric square forms in solution. Experimental and computational work on these latter assemblies is in progress.

Conclusion

These two sets of complementary porphyrin building blocks can be used for constructing diverse multi-porphyrin arrays in defined geometries through self-complementary or hetero-complementary assembly. The enthalpy of the latter is stronger by more than 2-fold, and this ensures that the self-complementary products are not complicating factors in the hetero self-assembly process. The 1-butyl-6-uracyl and 3,5-diacetamido-4-pyridyl groups can be used to form linear, square, and junction structures in a predefined metalation state. The ability to self-assemble nanoscaled building blocks with precisely controlled size and composition, and to incorporate them into larger electronics components—which may entail secondary self-assembly steps to form hierarchical structures—with unique properties and functions may have significant implications for the incorporation of these types of molecules into photonic devices. These studies also demonstrate that water can mediate the self-aggregation of H-bonding species and dictate the supramolecular arrangement of subunits, as it does in many protein structures.

Experimental Section

Materials and Methods.

Melting points were determined on a Thomas-Hoover UniMelt capillary apparatus and are uncorrected. Flash column chromatography was performed using 230–400 mesh ASTM Merck silica gel-60. ^1H and ^{13}C NMR spectra were recorded on JEOL 400 MHz, a Varian VXR-300 MHz, or a Varian 500 MHz instrument. Chemical shifts are reported in ppm relative to TMS for ^1H and ^{13}C spectra, and coupling constants in Hz. NMR assignments are consistent with those published previously. Agilent Technologies HP 1100 LC/MSD, and a Cary Bio-3 were used. Typical Electrospray Ionization Mass Spectroscopy (ESI-MS) method: $\sim 0.05 \text{ mM}$ solutions in acetonitrile/water(50:50) containing 1% trifluoroacetic acid, positive ion mode, and the fragmentor voltage between 100 and 350 V. Elemental analysis by Schwarzkopf Microanalytical Laboratory, Inc.

2,6-Diamino-4-methylpyridine (2).

A solution of 4-methylpyridine **1** (9.31 g, 9.73 mL, 0.10 mole) in 50 mL tetralin was added to a solution of sodium amide (9.33 g, 0.24 mole) in 100 mL tetralin at 130–140 °C over 6 h, afterward heated to 195 °C and kept at this temperature for 10 h. After cooling, the reaction mixture was filtered, and the remaining black solid material worked up by the dropwise addition of 150 mL ethanol. 10 g of silica gel was added, and the ethanol was removed under reduced pressure. The resultant dark solid was added to the top of a 45 g column of silica gel and eluted with ethyl acetate to afford 8.02 g (65%) of **2** as a white powder. Recrystallized from chloroform, mp 85–86 °C (lit. 87–88 °C, sublimed crystal, 109–111 °C). ¹H NMR(CDCl₃) δ 5.74 (s, 2H), 4.06 (br, s, 4H), 2.11 (s, 3H); ¹³C NMR(CDCl₃) δ 158.3, 151.3, 99.5, 21.8; MS (ESI) *m/z* (MH⁺, 124).

2,6-Diacetamido-4-methylpyridine (3).

16.0 mL of acetic anhydride was added to 1.5 g (12.2 mmol) of the diamine **2**. The resultant solution was stirred for 1 h and 2.35 g (93%) of a white crystalline solid **3** was collected by filtration, mp 199–201 °C. ¹H NMR(CDCl₃) δ 7.72 (s, 2H), 7.64 (br, m, 2H), 2.35 (s, 3H), 2.17 (s, 6H); ¹³C NMR(CDCl₃) δ 168.9, 153.4, 149.9, 110.9, 25.5, 22.5; MS (ESI) *m/z* (MH⁺, 208). Anal. Calcd for C₁₀H₁₃N₃O₂: C, 57.97; H, 6.32; N, 20.27. Found: C, 57.84; H, 6.50; N, 20.10.

2,6-Diacetamido-4-methylpyridine-1-oxide (4).

To a solution of the diamide **3** (2.07 g, 10.0 mmol) in 10 mL acetic acid, 3.0 mL of 32% peracetic acid was added carefully at room temperature. The resulting solution was heated for 3 h at 50–60 °C and 4 h at 65–70 °C. After cooling to room temperature, adding FeSO₄ solid to destroy residual oxidant, and removing the acetic acid under reduced pressure, the residue was recrystallized from water to yield 1.76 g (79%) of the oxide **4** as a white powder: mp 210–211 °C. ¹H NMR(CDCl₃) δ 9.83 (s, 2H), 7.92 (s, 2H), 2.35 (s, 3H), 2.27 (s, 6H); ¹³C NMR(CDCl₃) δ 164.4, 137.4, 137.0, 104.1, 21.0, 17.8; MS (ESI) *m/z* (MH⁺, 224). Anal. Calcd for C₁₀H₁₃N₃O₃: C, 53.80; H, 5.87; N, 18.82. Found: C, 53.94; H, 5.96; N, 18.90.

2-Diacetimido-6-acetamido-4-acetoxymethylpyridine (5).

A solution of the oxide **4** (1.50 g, 6.73 mmol) in acetic acid (3.0 mL) was added to stirred, refluxing acetic anhydride (20 mL) over a 30-min. period. The reaction mixture was stirred at reflux temperature for 30 h, cooled, 5.0 g silica gel was added to the reaction mixture, and the solvent removed under reduced pressure. The resultant dark material was added to the top of a 20 g column of silica gel and eluted with ethyl acetate/petroleum ether (1:1) to afford 1.49 g (72%) of **5** as a white powder, mp: 177–178 °C. ¹H NMR(CDCl₃) δ 8.24 (s, 1H), 7.89 (br, s, 1H), 6.93 (s, 1H), 5.17 (s, 2H), 2.29 (s, 6H), 2.21 (s, 3H), 2.20 (s, 3H); ¹³C NMR(CDCl₃) δ 172.9, 170.9, 169.2, 152.3, 151.7, 151.6, 118.0, 112.3, 64.7, 27.3, 25.5, 21.5; MS (ESI) *m/z* (MH⁺, 308). Anal. Calcd for C₁₄H₁₇N₃O₅: C, 54.72; H, 5.57; N, 13.67. Found: C, 54.66; H, 5.64; N, 13.71.

2,6-Diacetamido-4-hydroxymethylpyridine (6).

A solution of the acetate **5** (1.20 g, 3.9 mmol) and K₂CO₃ (0.59 g) in methanol/water (10 mL, 4:1) was stirred at room temperature for 8 h. The reaction mixture was loaded on 3.0 g silica gel. The resultant yellow material was added to the top of a 25 g column of silica gel and eluted with ethyl acetate/ethanol (9: 1) to afford 0.80 g (92%) of the alcohol **6** as a white powder, mp 194–195 °C. ¹H NMR(DMSO-*d*₆) δ 9.93 (s, 2H), 7.65 (s, 2H), 5.34 (t, 1H), 4.43 (d, 2H), 2.05 (s, 6H); ¹³C NMR(DMSO -*d*₆) δ 170.1, 156.8, 151.2, 107.5, 63.4, 25.2; MS (ESI) *m/z* (MH⁺, 224). Anal. Calcd for C₁₀ H₁₃ N₃O₃: C, 53.80; H, 5.87; N, 18.82. Found: C, 53.72; H, 6.04; N 18.86.

2,6-Diacetamido-4-formylpyridine (7).

A solution of the alcohol **6** (0.80 g, 3.58 mmol) in CH₂Cl₂ (15 mL) was treated with NaOAc (2.85 g, 14.32 mmol) followed by portion wise addition of pyridinium chlorochromate (PCC/Alumina, 1.15 g, 5.38 mmol). The reaction mixture was placed in a sonication bath at room temperature for 1 h, at which time additional PCC/Alumina (0.43 g, 2.01 mmol) was added. After being sonicated an additional 3 h, the reaction mixture was loaded on 3.0 g silica gel, added to the top of a 25 g column of silica gel, and eluted with ethyl acetate/ethanol (9:1) to afford 0.43 g (54%) of the aldehyde **7**, mp 223–224 °C. ¹H NMR(DMSO -*d*₆) δ 10.33 (s, 2H), 9.96 (s, 1H), 8.11 (s, 2H), 2.10 (s, 6H); ¹³C NMR(DMSO-*d*₆) δ 194.1, 170.7, 152.6, 146.5, 108.9, 25.3; MS (ESI) *m/z* (MH⁺, 222). Anal. Calcd for [C₁₀ H₁₂ N₃O₃]⁺: C, 54.05; H, 5.44; N, 18.91. Found: C, 53.63; H, 5.27; N, 18.26.

6-(Dimethoxymethyl)uracil(9).

A solution of orotaldehyde (**8**) (3.0 g, 21.42 mmol) and trimethyl orthoformate (9.08 g, 9.4 mL, 85.68 mmol) in MeOH (50 mL) and CH₂Cl₂ (100 mL) was refluxed for 10 h in the presence of *p*-toluenesulfonic acid (0.3 g, 1.58 mmol). After the reaction mixture cooled to room temperature, triethylamine was added to the reaction mixture until it turned weakly basic. 5.0 g silica gel was added to the reaction mixture and the solvent removed under reduced pressure. The resultant yellow material was added to the top of a 25 g column of silica gel and eluted with ethyl acetate/ethanol (9:1) to afford 3.46 g (87%) of the acetal **9** as a white powder, mp 185–186 °C, (lit.: 185–186 °C). ¹H NMR(CDCl₃) δ 11.02 (br, s, 1H), 10.83 (br, s, 1H), 5.45 (s, 1H), 4.99 (s, 1H), 3.25 (s, 6H); ¹³C NMR(CDCl₃) δ 164.9, 152.4, 151.8, 99.5, 99.1, 54.8; MS (ESI) *m/z* (M-H⁺, 185).

1-Butyl 1-6-(dimethoxymethyl)uracil (10).

To a solution of the acetal (**9**) (3.20 g, 17.20 mmol) in DMSO (200 mL) were added 1-bromobutane (0.7850 g, 0.62 mL, 5.73 mmol) and anhydrous K₂CO₃ (2.61 g, 18.92 mmol). The suspension was stirred for 72 h at room temperature after which it was filtered and the DMSO was removed in vacuo. The solid was absorbed on 5 g silica gel, loaded on the top of a 25 g column of silica gel, and eluted with hexane to afford 0.140 g (8.2%) of 1,3-dibutyl-6-(dimethoxymethyl)uracil as an oil. Further elution with ethyl acetate/hexane (1:9) afforded 0.222 g (16%) 3-butyl-6-(dimethoxymethyl)uracil and 0.513 g (37%) of **10**. Yields reported for this compound are based on 1-bromobutane, mp: 91–92 °C. ¹H NMR(CDCl₃) δ 9.28 (br, s, 1H), 5.95 (s, 1H), 5.05 (s, 1H), 3.87 (t, 2H, *J* = 7.7 Hz), 1.67–1.57, (m, 2H), 1.42–

1.30, (m, 2H), 0.95, (t, 3H, $J = 6.9$ Hz); ^{13}C NMR(CDCl₃) δ 163.4, 152.2, 151.3, 102.7, 99.9, 54.5, 45.1, 31.7, 20.8, 14.5; MS (ESI) m/z (MH⁺, 243).

1-Butyl-6-formyluracil (**11**).

A solution of the butylacetal **10** (0.50 g, 2.07 mmol) in 20 mL of CH₂Cl₂ was cooled to -78 °C and treated with 1.6 mL of BBr₃ and stirred for 2 h at that temperature. The cold bath was removed and the solution was allowed to reach room temperature. Saturated NaHCO₃ (15 mL) was added until the pH reached 7–7.5. The organic layer was removed and the aqueous layer was extracted with CH₂Cl₂. The extracts were combined and dried (with Na₂SO₄), and the solvent was removed to afford 0.315 g of the aldehyde **11** as a white solid (87%), mp 146–147 °C. ^1H NMR(CDCl₃) δ 9.57 (s, 1H), 9.18 (br, s, 1H), 6.25 (s, 1H), 4.19 (t, 2H, $J = 7.3$ Hz), 1.63–1.53, (m, 2H), 1.43–1.33, (m, 2H), 0.95, (t, 3H, $J = 7.3$ Hz); ^{13}C NMR(CDCl₃) δ 186.0, 162.6, 151.5, 147.6, 115.0, 44.5, 32.3, 20.5, 14.4; MS (ESI) m/z (M-H⁺, 195). Anal. Calcd for C₁₁H₁₈N₂O₄: C, 55.09; H, 6.16; N, 14.28. Found: C, 55.49; H, 6.13; N, 14.25.

5,10,15,20-Tetrakis (3,5-diacetamido-4-pyridyl)porphyrin (**VI**).

Pyrrole (69.5 μL , 1.0 mmol) and 2,6-diacetamido-4-formylpyridine **7** (221 mg, 1.0 mmol) were added to boiling propionic acid (10.0 mL). The reaction mixture was refluxed for 2 h and then taken to dryness under vacuum. The resulting solid was purified by chromatography on silica gel eluting with ethanol/ethyl acetate (1:1) to yield 77.1 mg (29%) of **VI**. ^1H NMR(DMSO-*d*₆) δ 10.52 (s, 8H), 8.99 (s, 8H), 8.60 (s, 8H), 2.16 (s, 24H), -3.10, (s, 2H); ^{13}C NMR(DMSO-*d*₆) δ 170.7, 153.2, 150.1, 132.7, 119.4, 116.5, 25.4; MS (ESI) m/z (MH⁺, 1075). Anal. Calcd for [C₅₆H₅₀N₁₆O₈ plus 2 H₂O] C, 60.45; H, 4.89; N, 20.16. Found: C, 60.92; H, 4.95; N, 20.01.

Diacetamidopyridyl/*tert*-butylphenyl Porphyrins.

2,6-diacetamido-4-formylpyridine **7** (2.763 g, 12.5 mmol) and 4-*tert*-butylbenzaldehyde (1.63 g, 1.68 mL, 10.0 mmol) were added to 450 mL of boiling propionic acid and then 1.56 mL (22.6 mmol) of pyrrole was added. The reaction mixture was refluxed for 2 h at which time a 23.8% yield of the mixture of porphyrins was detected spectroscopically. The solvent was removed under vacuum, and the resulting solid was purified by chromatography eluting with hexane (**I**), to chloroform (**II**), chloroform/ethyl acetate (1:1) (**III**, **IV**), and ethyl acetate (**V**, **VI**) to get the four porphyrins with two different motifs at the *meso* positions. A second column using 10% v/v dioxane in chloroform is used to purify the fractions containing both **III** and **IV**, and typically the tetra substituted derivatives are not isolated as they can be made directly. Based on starting pyrrole, the isolated yield is 20.6%, and the isolated amounts are **I**, 0.153 g (3.5%); **II**, 0.261 g (5.14%); **III**, 0.222 g (4.11%); **IV**, 0.290 g (5.36%); **V**, 0.149 g (2.60%); **VI**, 0.052 g (0.86%). The relative amounts are **II** (24%), **III** (20%), **IV** (26%), and **V** (11%), and the two homo-substituted porphyrins **I** (14.5%) and **VI** (4.5%).

5-(3,5-Diacetamido-4-pyridyl)-10,15,20-tris (4-*tert*-butylphenyl)porphyrin (II).

^1H NMR(CDCl_3) [500 MHz NMR, 50 °C] δ 9.11, 9.05 (d, 2H, $J = 5.0$ Hz), 8.92 (s, 4H), 8.81 (s, 2H), 8.89 (s, 2H), 8.175, 7.785 (d, 12 H, $J = 7.5$ Hz), 2.298 (s, 6H), 1.637 (s, 27 H), -2.761 (s, 2H); ^{13}C NMR($\text{DMSO}-d_6$) δ 169.0, 156.1, 151.1, 148.4, 139.7, 135.1, 131.7–131.9, 124.2, 121.6, 121.2, 117.0, 35.7, 32.5, 25.6; MS (ESI) m/z (MH^+ , 898).

5,15-Bis(3,5-diacetamido-4-pyridyl)-10,20-bis(4-*tert*-butylphenyl) porphyrin (III).

^1H NMR(CDCl_3) δ 9.27, 9.23 (dd, 8H, $J = 4.4$), 9.15 (s, 4H), 8.49, 8.10 (d, 8H, $J = 8.1$), 8.35 (s, 4H), 2.62 (s, 12 H), 1.95 (s, 18 H), -2.49 (s, 2H); MS (ESI) m/z (MH^+ , 957).

5,10-Bis(3,5-diacetamido-4-pyridyl)-15,20-bis(4-*tert*-butylphenyl) porphyrin (IV).

^1H NMR(CDCl_3) [500 MHz NMR, 50 °C] δ 8.98 (s, 2H), 8.95, 8.91 (dd, 4H, $J = 5.0$ Hz), 8.89 (s, 2H), 8.77 (s, 2H), 7.90 (s, 2H), 8.17, 7.79 (d, 8H, $J = 7.5$ Hz), 2.29 (s, 6H), 1.64 (s, 27 H), -2.72 (s, 2H); ^{13}C NMR($\text{DMSO}-d_6$) δ 170.3, 150.9, 149.6, 138.6, 134.7, 131.2–132.6, 124.3, 121.5, 117.9, 115.8, 35.1, 31.9, 24.7; MS (ESI) m/z (MH^+ , 957).

5,10,15-Tris(3,5-diacetamido-4-pyridyl)-20-(4-*tert*-butylphenyl) porphyrin (V).

^1H NMR($\text{DMSO}-d_6$) δ 10.51 (s, 6H), 8.81–8.97 (m, 8H), 8.59 (s, 6H), 8.12, 7.77 (dd, 4H, $J = 8.1$), 2.16 (s, 18 H), 1.51 (s, 18 H), -3.10 (s, 2 H); ^{13}C NMR($\text{DMSO}-d_6$) δ 170.8, 153.5, 151.4, 150.1, 138.9, 135.2, 132.4–132.5, 129.9, 129.2, 126.3, 124.7, 122.3, 119.2, 116.4, 35.7, 32.5, 25.4; MS (ESI) m/z (MH^+ , 1016).

5,10,15,20-Tetrakis(1'-butyl-6'-uracyl)porphyrinato-(Zn)(II) (XII).

Pyrrole (69.5 μL , 1.0 mmol), 1-butyl-6-formyl-uracil (196 mg, 1.0 mmol) and zinc acetate (109.8 mg, 0.50 mmol) were added to a boiling mixture of acetic acid (7.5 mL) and nitrobenzene (5.0 mL). The reaction mixture was refluxed for 10 h while monitoring the yields spectroscopically, and then taken to dryness under vacuum. The resulting solid was purified by chromatography, eluting with ethyl acetate to afford ~5.1% **12**. ^1H NMR($\text{DMSO}-d_6$) δ 11.83 (br, s, 4H), 9.50 (m, 8H), 6.26 (s, 4H), 3.56–3.08 (m, 8H), 1.10–0.91 (m, 8H), 0.30–0.08 (m, 8H), 0.00–-0.60 (m, 12 H); ^{13}C NMR(CDCl_3) δ 185.0, 163.4, 150.6, 142.3, 110.4, 41.9, 30.3, 20.9, 14.5; MS (ESI) m/z (MH^+ , 1037 for ZnXII). Anal. Calcd for $\text{C}_{52}\text{H}_{52}\text{N}_{12}\text{O}_8\text{-Zn}$: C, 60.15; H, 5.05; N, 16.18, for $\text{C}_{52}\text{H}_{52}\text{N}_{12}\text{O}_8\text{Zn}$ with 1 H_2O : C, 59.12; H, 5.16; N, 15.90. Found: C, 60.04; H, 5.24; N 15.92.

Uracyl/*tert*-Butylphenyl Porphyrins.

Pyrrole (0.83 mL, 12.0 mmol), 1-butyl-6-formyluracil (1.568 g, 8.0 mmol) and zinc acetate (2.90 g, 13.2 mmol) were added to a boiling mixture of acetic acid (90.0 mL) and nitrobenzene (60.0 mL). After 10 min, 4-*tert*-butylbenzaldehyde (0.652 g, 0.67 mL, 4.0 mmol) was added to the reaction mixture and reflux continued for 10 h. A 22.4% overall yield of the mixture of porphyrins was detected spectroscopically in the reaction mixture. The solvent was removed under vacuum. The resulting solid was purified by chromatography using a solvent gradient (isolated yield, % yield based on starting pyrrole): starting with hexane **I** (0.075 g, 2.37%), then chloroform **VIII** (0.225 g, 6.44%), then chloroform/ethyl acetate (1:1) **IX** (0.08 g, 2.21%), and **X** (0.10 g, 2.76%), and ethyl acetate

XI (0.02 g, 0.51%), and **XII** (5 mg, 0.12%) to get the foururacyl/phenyl porphyrins. A second column using a 15% v/v dioxane/chloroform solution as eluent can be used to separate **IX**, **X**, and their rotameric forms. An ~18%, 0.5 g, isolated yield is obtained for the collection of porphyrins with relative yields of **I**, 15%; **VIII**, 45%; **IX**, 15%; **X**, 20%; **XI**, 4%; **XII**, 1%. Typically the tetra substituted derivatives are not isolated as they can be made directly.

5-(1'-Butyl-6'-uracyl)-10,15,20-tris (4-*tert*-butylphenyl)-porphyrin (VIII**).**

¹H NMR(CDCl₃) [500 MHz NMR] δ 9.11, 9.05 (dd, 4H, J = 4.5 Hz), 8.92 (s, 4H), 8.81 (s, 1H), 8.12~8.22, 7.81~7.84 (m, 12 H), 6.60 (s, 1H), 3.47 (t, 2H, J = 8.0 Hz), 1.20 (m, 2H), 0.41(m, 2H), 0.08(t, 3H, J = 7.5 Hz); ¹³C NMR(CDCl₃) δ 162.5, 156.9, 151.6, 151.7, 139.4, 135.1, 129.2~132.6, 124.5, 124.3, 123.56, 122.16, 110.31, 106.81, 47.62, 35.74, 32.48, 31.82, 19.94, 13.65; MS (ESI) m/z (MH⁺, 873).

5,15-Bis(1'-butyl-6'-uracyl)-10,20-bis(4-*tert*-butylphenyl)-porphyrinato(Zn)(II) (IX**).**

¹H NMR(DMSO-*d*₆): (**IXa**) R/ β rotamer(CDCl₃) 11.84 (s, 4H), 9.32, 8.83 (dd, 8H, J = 4.8 Hz), 8.08, 7.81 (2d, 8H, J = 8.2 Hz), 6.21 (s, 2H), 3.20~3.32 (m, 4H), 1.56 (s, 18 H), 1.05~1.10 (m, 4H) 0.21~0.23 (m, 4H), -0.20 (t, 6H, J = 7.33 Hz); MS (ESI) m/z (MH⁺, 907).

(**IXb**) RRrotamer(CDCl₃) 11.84(s, 4H), 9.32, 8.82 (dd, 8H, J = 4.76), 8.09, 7.77 (2d, 8H, J = 7.3 Hz), 6.23 (s, 2H), 3.21~3.34 (m, 4H), 1.54 (s, 18 H), 1.03~1.08 (m, 4H) 0.31~0.35 (m, 4H), -0.11 (t, 6H, J = 7.32); MS (ESI) m/z (MH⁺, 907).

5,10-Bis(1'-butyl-6'-uracyl)-15,20-bis(4-*tert*-butylphenyl)-porphyrinato (Zn)(II) (X**).**

¹H NMR(DMSO-*d*₆) 11.81 (s, 1H), 9.26, 8.79 (d, 4H, J = 4.8 Hz), 8.75 (s, 4H), 8.12~7.77 (m, 12 H), 6.27 (s, 2H), 3.22~3.34 (m, 2H), 1.55 (s, 27 H), 1.01~1.08 (m, 2H), 0.19~0.26 (m, 2H), -0.18 (t, 3H, J = 7.32 Hz); ¹³C NMR (CDCl₃) δ 162.00, 156.10, 151.13, 148.42, 139.75, 135.14, 131.70~131.88, 124.21, 121.64, 121.15, 116.97, 35.68, 32.48, 25.58; MS (ESI) m/z (MH⁺, 907).

Supplementary Material

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Figure 1.
Interactions between two porphyrin building blocks via complementary hydrogen bonding.
Assemblies containing more than two uracyl groups will have one or more isomeric forms.

Figure 2.

Top: Molecular structure and atom names for **IV**. Thermal ellipsoids are drawn at the 50% probability level. Peripheral hydrogens are omitted for clarity. Middle : Dis-placements of the 24 atoms that comprise the macrocycle from the 24 atom mean porphyrin plane in units of 0.01 Å. Bottom: Edge-on view of the porphyrin core. Thermal ellipsoids enclose 1% probability for clarity.

Figure 3.
Hydrogen-bonded supramolecular assembly of porphyrin **IV** mediated by water. (Hydrogen bonds are shown as dotted lines.)

Figure 4. Formation of closed tetrameric squares. (A) The self-complementary association of **IV** in CDCl_3 is compared to (B) the complementary association of a 1:1 mixture of **IV** and **X** in THFd_8 .

Scheme 1

Scheme 2

Scheme 3

Scheme 4

Scheme 5