Synthesis of Near-IR Absorbing/Emitting Porphyrazine Derivatives with Tunable Solubility

Sangwan Lee,[†] Andrew J. P. White,[‡] David J. Williams,[‡] Anthony G. M. Barrett,*[,‡] and Brian M. Hoffman*[,†]

Departments of Chemistry, Northwestern University, Evanston, Illinois 60208-3113, and Imperial College of Science, Technology and Medicine, London SW7 2AY, England

bmh@new.edu

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We report the synthesis of porphyrazines (pzs), or tetraazaporphyrins, of the form H_2[pz(**A**$_n$;**B**$_{4-n}$)], where **A** is [S(CH_2)$_3$COOR]$_2$ (R = *n*-Pr, H) and **B** is a fused *β*,*β*′-diisopropyloxybenzo group, including the compounds with $n = 4$ (**6**), $n = 3$ (**7**) and the *trans* compound with $n = 2$ (**8**) (Scheme 1). The synthesis employs Linstead crossover macrocyclization of dimethyl 6,7-dicyano-5,8-dithia-6(*Z*)-dodecenedioate, MNT(C_4O_2Me)$_2$ (**2**), with 1-imino-4,7-bis(1-methylethoxy)-1*H*-isoindole-3-amine (**4**). These pigments were characterized by ^{1}H NMR, ^{13}C NMR, absorbance/fluorescence spectroscopy, mass spectrometry, and microanalysis. An X-ray crystal structure of **8** is presented. Of particular note, **6**−**8** display intense near-IR absorbance and dual UV−visible/near-IR emission which are very important in potential biomedical applications, both for cancer therapy (photodyanamic therapy, PDT) and cancer diagnosis (optical tumor imaging). For example, the *trans*-porphyrazine **8** has an intense long-wavelength absorption at ca. 800 nm (log $\epsilon = 4.18$) and S1 fluorescence at ∼820 nm, where mammalian tissue is effectively penetrated by light. Transformation of the ester group permits a wide range of functionality and solubility to be generated without change in optical properties. As an example, hydrolysis of these compounds by LiOH in THF/H_2O gives the corresponding carboxylato-functionalized pigments **9**−**11**, which are described. The last of these dissolves without aggregation in fetal calf serum.

Introduction

Porphyrazines (pzs), or tetraazaporphyrins, are porphyrinic macrocycles in which the meso positions contain nitrogens, not CH,[1] and are of potential interest for a wide variety of applications.[2−9] The pzs are prepared by an entirely different synthetic route than porphyrins, by template cyclization of maleonitrile derivatives, rather than the condensation of pyrrole derivatives and aldehydes. The pz synthetic route allows the straightforward synthesis of macrocycles with chemical and physical properties not readily accessible to porphyrins. In particular, pzs with S, N, or O heteroatoms attached to the porphyrin-like macrocycle core are readily synthesized,[10−15] and porphyrazines that bear two different kinds of substituents can be prepared by the cocyclization of two different dinitriles.[11,13,14,16−23] Here we report the synthesis and characterization of a series of porphyrazines of the form H_2[pz(**A**$_n$;**B**$_{4-n}$)] (Scheme 1) where **A** is [S(CH_2)$_3$COOR]$_2$ (R = *n*-Pr, H) and **B** is a fused *β*,*β*′-diisopropyloxybenzo group. The synthesis employs Linstead crossover macrocyclization of MNT(C_4O_2Me)$_2$ (**2**) with 1-imino-4,7-bis(1-methylethoxy)-1*H*-isoindole-3-amine (**4**), and we describe macrocycles with $n = 4$ (**6**), $n = 3$ (**7**), and $n = 2$ (**8**).

[†] Northwestern University.

[‡] Imperial College of Science, Technology and Medicine.

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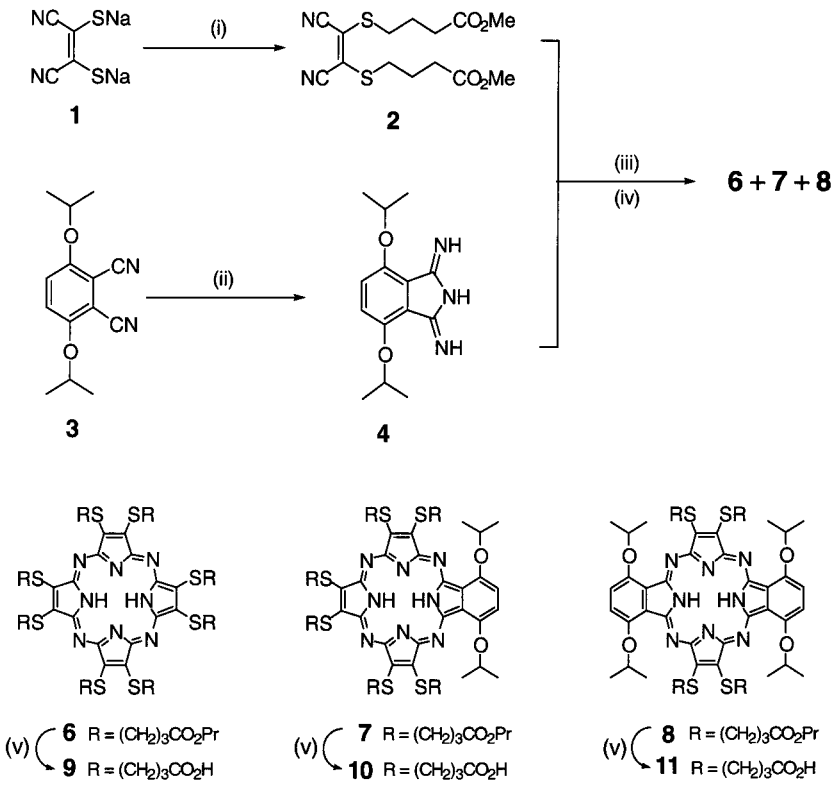
Scheme I[a]



[a] Key: (i) $Cl(CH_2)_3CO_2CH_3$, NaI, acetone at reflux, 24 h; (ii) NH_3(g), Na, *n*-PrOH at reflux, 12 h; (iii) $Mg(OPr)_2$, *n*-PrOH at reflux, 7 h; (iv) TFA, CH_2Cl_2, 20 °C, 1 h; (v) LiOH, THF/H_2O, 20 °C, 4−5 days.

Of particular note, **6**−**8** display intense near-IR absorbance and dual UV−visible/near-IR emission which are very important in potential biomedical applications, for both cancer therapy (photodyanamic therapy, PDT) and cancer diagnosis (optical tumor imaging). For example, the *trans*-porphyrazine **8** has an intense long-wavelength absorption at ca. 800 nm and S1 fluorescence at ∼820 nm, at which mammalian tissue is weakly absorbing.[24] Transformation of the ester group permits a wide range of functionality and solubility to be generated without change in optical properties. As an example, hydrolysis[25] of these compounds by LiOH in THF/H_2O gives the corresponding carboxylato-functionalized pigments **9**−**11**, which also are described.

Results and Discussion

Synthesis. The general synthesis of the H_2[pz(**A**$_n$;**B**$_{4-n}$)] is shown in Scheme 1. $MNT(C_4O_2Me)_2$ (**2**) was prepared by treating disodium 1,2-dicyano-1,2-ethenedithiolate, Na_2MNT (**1**), with 2 equiv of methyl 4-chlorobutanoate in the presence of a catalytic amount of NaI in acetone at reflux for 1 day. 1-Imino-4,7-bis(1-methylethoxy)-1*H*-isoindole-3-amine (**4**) was obtained via the imidation of 3,6-bis(1-methylethoxy)-1,2-benzenedicarbonitrile (**3**) by bubbling ammonia gas through a hot solution of *n*-propanol at reflux. The use of *n*-propanol as reaction medium improved the yield and purity over the prior use of ethylene glycol.[14]

H_2[pz(A$_n$;B$_{4-n}$)] Porphyrazines 6−8. Magnesium-template cyclization[26] of a mixture of **2** and **4** in a 1:6 stoichiometric ratio, followed by demetalation with trifluoroacetic acid and purification, produced H_2[pz(**A**$_3$;**B**)] (**7**) and *trans*-H_2[pz(**A**$_2$;**B**$_2$)] (**8**) in 5% and 7% yields, respectively, along with trace amounts of H_2[pz(**A**$_4$)] (**6**). None of the *cis*-H_2[pz(**A**$_2$;**B**$_2$)] pigment was detected, nor was any H_2[pz(**B**$_4$)] formed. The high ratio of **2** to **4** was required because **2** is much more reactive than the diiminoisoindoline **4**. An alternate procedure, gradual addition of **2** into a mixture of **4** and $Mg(OPr)_2$ in *n*-propanol, allowed us to reduce the amount of **2** to the ratio of 1:3 (**2**:**4**) and increased the yield of **8** (10%). During cyclization in *n*-propanol, the methyl ester was converted to the *n*-propyl ester by transesterification. All the H_2pzs can be metalated (e.g., Cu[pz(**A**$_4$)] (**5**)) by standard procedures.[27]

Hydrolysis of Porphyrazines 6−8 to the Corresponding Acids 9−11. Hydrolysis of porphyrazines **6**−**8** using an excess (>4 equiv) of lithium hydroxide in THF/H_2O yielded the corresponding carboxylic acids **9**−**11**, as shown in Scheme 1. The carboxylic acids **9**−**11** are insoluble in organic solvents but soluble in pyridine and in basic aqueous media (pH >7.4). In addition, **9**−**11** can be transformed to esters or amides to further alter the solubility.

X-ray Crystal Structure of 1,4,13,16-Tetrakis(1-methylethoxy)-8,9,20,21-tetrakis[(4-(propyloxy)-4-oxo-1-butyl)thio]-25*H*,27*H*-dibenzo[*b*,*l*]porphyrazine (8). Black platelike needles of **8** were grown from

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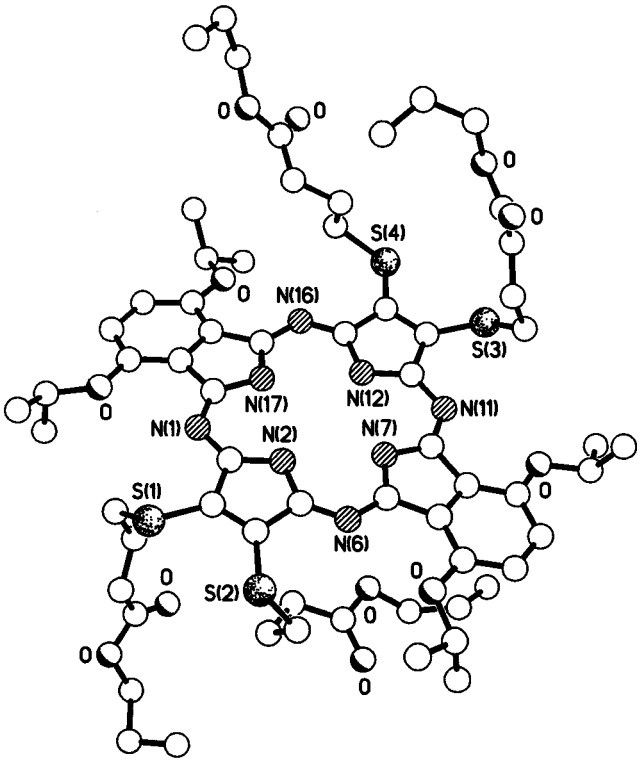

Figure 1. Molecular structure of one of the three crystallographically independent molecules (**I**) present in the structure of **8**.

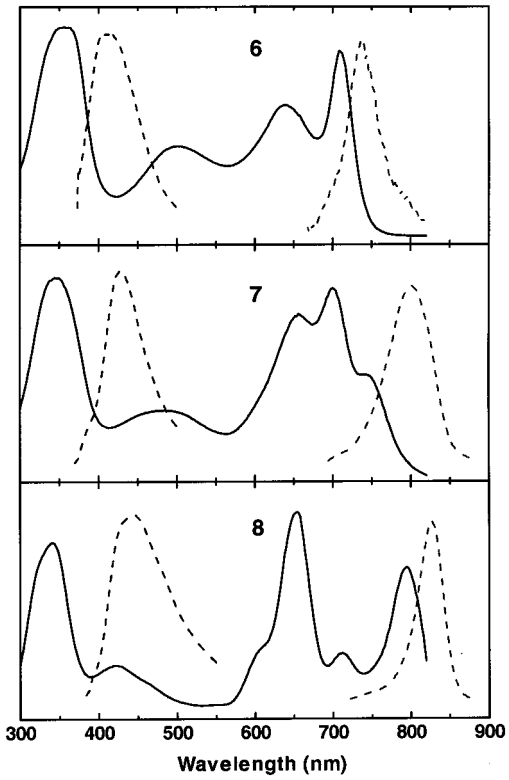

Figure 2. Absorbance/fluorescence spectra (CH_2Cl_2) of **6**−**8**.

CH_2Cl_2/MeOH solution. X-ray analysis showed the crystals to contain three crystallographically independent molecules (**I**−**III**) in the asymmetric unit (Figure S1; Supporting Information). Each molecule has a different conformation, with molecules **II** and **III** having all four of their "tentacle-like" ester side chains lying on one side of the porphyrazine ring plane, while in molecule **I** two lie above and two lie beneath (Figure 1). In molecule **I** the two benzpyrrole ring systems are folded by ca. 15° to each other, while the two sulfur-bearing pyrrole rings are coplanar (to within 1°); the four pyrrole nitrogen atoms are coplanar to within 0.05 Å. In **II** the benzpyrrole rings are inclined by ca. 19°, whereas the two pyrrole rings are folded by ca. 19° in the opposite sense (i.e. a tetrahedral type distortion); the four pyrrole nitrogen atoms are still coplanar to within 0.06 Å. In **III** there is disorder in a substantial portion of the porphyrazine core with two slightly tilted orientations being observed; here both the benzpyrrole and pyrrole ring systems appear to have closer to planar conformations.

Electronic Absorption and Emission Spectra. The 4-fold symmetric porphyrazines show an intense B (Soret) band at λ < 400 nm and a single Q-band that has its principal absorption at λ > 600 nm, whereas porphyrazines with reduced symmetry show a split Q-band.[28] Figure 2 presents absorbance spectra of **6**−**8**, all dissolved in CH_2Cl_2. Although **6** is symmetrically substituted, as usual the internal protons break the symmetry and split the single Q-band seen at 690 nm for Cu[pz($\mathbf{A}_4$)] (**5**).[13] In addition, **5** and **6** show an absorbance at ∼500 nm that has been assigned to n−π* transitions that originate in the lone-pair orbitals on sulfur.[13] The periphery of **7** is unsymmetrically substituted, and its split Q-band is shifted somewhat to the red, while the intensity of the n−π* transitions is reduced, as seen in analogously substituted compounds.[15] The *trans*-porphyrazine **8** has an extremely sharp, well-defined split pair of Q-bands (654, 798 nm; Figure 2) which show a greater red shift and a larger splitting (2710 cm^{-1}) than those of corresponding alkyl, nitrogen, or oxygen-substituted pigments.[14] When the acids **9**−**11** are dissolved in organic solvents (e.g., DMSO), they show identical spectra; the same is true for aqueous media, except for broadening or slight peak shifts at pH values below ∼7.4 due to aggregation.

The emission spectra of **6**−**8** in CH_2Cl_2, all taken with short-wavelength excitation (λ_{max} ∼340 nm) also are presented in Figure 2. As has been seen for other porphyrinic compounds,[28] these pzs display dual emission, with peaks from S2 fluorescence at λ_{max} = 463, 428, 440 nm for **6**−**8**, respectively, and from S1 fluorescence at λ_{max} = 766, 800, 827 nm, respectively. Again, emission spectra for acids **9**−**11** in CH_2Cl_2 correspond to those of their ester counterparts.

To test the solubility and optical characteristics of these porphyrazines in biological fluids, we examined **11** dissolved in fetal calf serum (FCS), as well as FCS that had been "spiked" with hemoglobin, whose absorbance stops light transmission through tissue at wavelengths less than ∼650−700 nm. Figure 3 shows the spectrum of (a) fetal calf serum (FCS), (b) ∼10 μM **11** in FCS, (c) ∼60 μM HbCO (which is stable to handling) in FCS, and (d) **11** plus HbCO. Although the serum absorbs strongly at short wavelengths and has a substantial tailing absorption well past 800 nm, the spectrum shows that the Q-band of **11** could be detected easily by absorption, down to ∼1 μM. The figure further shows that **11** fluoresces strongly at ∼800 nm when dissolved in FCS; its detection

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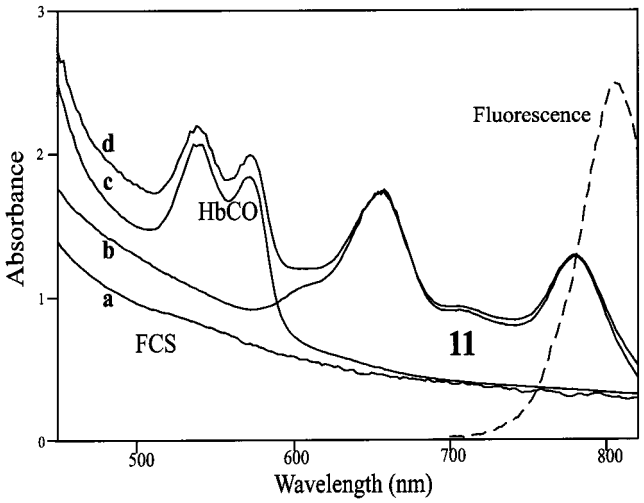

Figure 3. Optical spectra of (a) fetal calf serum (FCS), (b) **11** (~10 μM) in FCS, (c) hemoglobin-CO (HbCO) (~60 μM) in FCS, and (d) **11** (~10 μM) plus HbCO (~60 μM) in FCS.

limit by fluorescence would be much lower. The equivalence of the absorbance/emission for **11** dissolved in CH_2Cl_2 and FCS shows that **11** does not aggregate in FCS.

Conclusions

We have prepared macrocycles **6**−**8** which display intense near-IR absorbances and dual emission, including fluorescence in the near-IR, properties which are very important in potential biomedical applications (see, for example, ref 29). A wide range of functionality and solubilities can be generated through transformation of the ester group without change in optical properties. This is illustrated by the preparation of the carboxylic acid derivatives **9**−**11**, which are soluble in aqueous and biological media. Other transformations of the ester group will be reported in due course.

Experimental Section

General Considerations. All reagents were obtained from Aldrich Chemical Co. and used without further purification. 1-Imino-4,7-bis(1-methylethoxy)-1*H*-isoindole-3-amine (**4**) was prepared by a modification of the literature method;[14] the use of *n*-propanol as the solvent improved the yield. Electronic absorption spectra were recorded on a Hewlett-Packard HP8452A diode-array spectrophotometer and a Varian Cary 1E UV−visible spectrometer. Electronic emission spectra were recorded using a Photon Technology International QM2 fluorescence spectrometer. ^{1}H and ^{13}C NMR spectra were obtained using either a Varian Gemini 300 or a Varian Inova 500 spectrometer. Both electron spray ionization mass spectra (ESI-MS) and atmospheric phase chemical ionization mass spectra (APCI-MS) were acquired on a Micromass Quattro II LC-MS/MS mass spectrometer. Elemental analyses were performed by Oneida Research Services, Whiteboro, NY.

Dimethyl 6,7-Dicyano-5,8-dithia-6(*Z*)-dodecenedioate (2). A mixture of disodium 1,2-dicyano-1,2-ethenedithiolate, Na_2MNT (**1**;[30] 18.6 g, 0.1 mol), methyl 4-chlorobutanoate (28.6 g, 0.2 mol), and NaI (6.9 g, 0.04 mol) in dry acetone (300 mL) was heated at reflux for 24 h under N_2. After the reaction was complete, the mixture was cooled to room temperature and filtered. The filtrate was rotary-evaporated, and the residue was dissolved in CH_2Cl_2 (100 mL) and washed with a large amount of water to remove water-soluble materials. The organic phase was separated, dried (Na_2SO_4), and rotary-evaporated. Chromatography of the resultant oil on silica gel (CH_2Cl_2 eluant) gave dinitrile **2** (22.3 g, 65.2%) as a viscous yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.06 (tt, J = 7.3 Hz, J = 7.1 Hz, 4H, $SCH_2CH_2CH_2$), 2.49 (t, J = 7.1 Hz, 4H, $SCH_2CH_2CH_2CH_2$), 3.20 (t, J = 7.3 Hz, 4H, $SCH_2CH_2CH_2$), 3.70 (s, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.2, 32.2, 34.2, 52.0, 112.0, 121.3, 172.7; IR ν_{max} (neat, cm^{-1}) 2210, 1735; ESI-MS (*m*/*z*) calcd for $C_{14}H_{19}N_2O_4S_2$ [M + H]$^+$ 343.08, found 343. Anal. Calcd for $C_{14}H_{18}N_2O_4S_2$: C, 49.11; H, 5.30; N, 8.18. Found: C, 49.05; H, 5.31; N, 8.21.

1-Imino-4,7-bis(1-methylethoxy)-1*H*-isoindole-3-amine (4). 3,6-Bis(1-methylethoxy)-1,2-benzenedicarbonitrile (**3**; 24.4 g, 0.1 mol) was suspended in *n*-PrOH (500 mL), freshly cut Na (0.5 g) was added, and the mixture was heated in an oil bath under N_2. NH_3(g) was bubbled through the solution for 12 h while maintaining the solvent at reflux. The volume was reduced to approximately one-fourth by distillation of *n*-PrOH, and the hot concentrated solution was cooled to room temperature overnight. This yielded a chunky pale brown solid (18.1 g), which was collected by filtration and washed with a large amount of water. The filtrate was poured into a large volume of water, precipitating additional **4** (7.5 g). The solid products were combined and purified by recrystallization (MeOH−EtOH) to yield the diiminoisoindoline **4** (22.9 g, 87.7%) as a pale brown solid. Analytical data are as previously reported.[14]

H_2[pz(A_n;B_{4-n})] Porphyrazines 6−8. Mg turnings (0.1 g, 4.1 mmol) and I_2 (0.01 g) in *n*-PrOH (100 mL) were heated under reflux for 24 h under N_2 to prepare $Mg(OPr)_2$. MNT(C_4O_2Me)$_2$ (**2**; 0.52 g, 1.52 mmol) and diiminoisoindoline (**4**; 2.38 g, 9.12 mmol) were added, and the suspension was heated under reflux for 7 h. The solution immediately turned a dark brown color and finally to green-black. The solvent was distilled off under reduced pressure, and the green-black residue was dissolved in CH_2Cl_2 (100 mL). TFA (5 mL) was slowly added to the green-black solution, and the solution was stirred at room temperature for 1 h and diluted with CH_2Cl_2 (100 mL). The mixture was neutralized with dilute $NaHCO_3$(aq), washed with a large amount of water to remove TFA and other water-soluble materials, dried (Na_2SO_4), and rotary-evaporated. The resulting residue was chromatographed on silica gel (eluant AcOEt/CH_2Cl_2 = 1/19) to provide porphyrazines **6**−**8**. The pigments eluted in the order **8**, **7**, and **6**, and each was further purified by recrystallization from CH_2Cl_2−MeOH.

2,3,7,8,12,13,17,18-Octakis[(4-propyloxy-4-oxo-1-butyl)thio]-21*H*,23*H*-porphyrazine (6). MNT(C_4O_2Me)$_2$ (**2**) was macrocyclized in the presence of $Mg(OPr)_2$ in *n*-PrOH following the method described previously for the porphyrazines **6**−**8** to give the title compound **6** (20−22% yield): UV−vis (CH_2Cl_2) λ_{max} (log ϵ) 356 (4.66), 498 (2.23), 638 (3.01), 709 (3.99) nm; ^{1}H NMR (300 MHz, $CDCl_3$) δ −1.18 (br s, 2H, N*H*), 0.84 (t, J = 7.4 Hz, 24H, $OCH_2CH_2CH_3$), 1.55 (m, 16H, $OCH_2CH_2CH_3$), 2.20 (tt, J = 7.3 Hz, J = 7.1 Hz, 16H, $SCH_2CH_2CH_2$), 2.68 (t, J = 7.3 Hz, 16H, $SCH_2CH_2CH_2$), 3.96 (t, J = 6.7 Hz, 16H, $OCH_2CH_2CH_3$), 4.15 (t, J = 7.1 Hz, 16H, $SCH_2CH_2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.5, 22.1, 25.9, 33.2, 34.6, 66.3, 140.6, 153.8, 173.2; ESI-MS (*m*/*z*) calcd for $C_{72}H_{107}N_8O_{16}S_8$ [M + H]$^+$ 1595.56, found 1595. Anal. Calcd for $C_{72}H_{106}N_8O_{16}S_8$: C, 54.18; H, 6.69; N, 7.02. Found: C, 54.12; H, 6.67; N, 7.09.

19,22-Bis(1-methylethoxy)-4,5,9,10,14,15-hexakis[(4-propyloxy-4-oxo-1-butyl)thio]-23*H*,25*H*-porphyrazine (7): yield 109 mg, 0.076 mmol, 5%; UV−vis (CH_2Cl_2) λ_{max} (log ϵ) 346 (4.61), 656 (3.77), 700 (4.34), 744 (sh) nm; ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.23 (br s, 2H, N*H*), 0.76 (t, J = 7.4 Hz, 6H, $OCH_2CH_2CH_3$), 0.83 (t, J = 7.4 Hz, 6H, $OCH_2CH_2CH_3$), 0.83 (t, J = 7.4 Hz, 6H, $OCH_2CH_2CH_3$), 1.45 (qt, J = 7.4 Hz, J = 6.8 Hz, 4H, $OCH_2CH_2CH_3$), 1.54 (qt, J = 7.4 Hz, J = 6.8 Hz, 4H, $OCH_2CH_2CH_3$), 1.54 (qt, J = 7.4 Hz, J = 6.8 Hz, 4H, $OCH_2CH_2CH_3$), 1.81 (d, J = 5.9 Hz, 12H, $CHMe_2$), 2.01 (tt, J = 7.1 Hz, J = 6.9 Hz, 4H, $SCH_2CH_2CH_2$), 2.20 (tt, J = 7.1 Hz, J = 6.9 Hz, 4H, $SCH_2CH_2CH_2$), 2.21 (tt, J = 7.1 Hz, J = 6.9

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Hz, 4H, $SCH_2CH_2CH_2$), 2.58 (t, J = 7.1 Hz, 4H, $SCH_2CH_2CH_2$), 2.67 (t, J = 7.1 Hz, 4H, $SCH_2CH_2CH_2$), 2.67 (t, J = 7.1 Hz, 4H, $SCH_2CH_2CH_2$), 3.85 (t, J = 6.8 Hz, 4H, $OCH_2CH_2CH_3$), 3.96 (t, J = 6.8 Hz, 4H, $OCH_2CH_2CH_3$), 3.96 (t, J = 6.8 Hz, 4H, $OCH_2CH_2CH_3$), 4.05 (t, J = 6.9 Hz, 4H, $SCH_2CH_2CH_2$), 4.11 (t, J = 6.9 Hz, 4H, $SCH_2CH_2CH_2$), 4.20 (t, J = 6.9 Hz, 4H, $SCH_2CH_2CH_2$), 5.28 (hp, J = 5.9 Hz, 2H, $CHMe_2$), 7.66 (s, 2H, Ar *H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.4, 10.5, 22.0, 22.1, 22.9, 25.7, 25.8, 25.9, 33.0, 33.2, 33.3, 34.6, 34.7, 34.8, 66.08, 66.16, 66.18, 72.7, 119.6, 126.9, 138.2, 139.1, 142.3, 150.5, 151.0, 152.0, 154.2, 155.0, 173.2, 173.3; APCI-MS (*m*/*z*) calcd for $C_{68}H_{97}N_8O_{14}S_6$ $[M + H]^+$ 1441.54, found 1441.3. Anal. Calcd for $C_{68}H_{96}N_8O_{14}S_6$: C, 56.64; H, 6.71; N, 7.70. Found: C, 56.18; H, 6.63; N, 7.85.

1,4,13,16-Tetrakis(1-methylethoxy)-8,9,20,21-tetrakis-[(4-propyloxy-4-oxo-1-butyl)thio]-25*H*,27*H*-dibenzo[*b*,*l*]-porphyrazine (8): yield 136 mg, 0.106 mmol, 7%; UV−vis (CH_2Cl_2) λ_{max} (log ϵ) 340 (4.80), 422 (1.96), 654 (5.49), 712 (2.22), 798 (4.18) nm; ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.51 (br s, 2H, N*H*), 0.74 (t, J = 7.4 Hz, 12H, $OCH_2CH_2CH_3$), 1.43 (m, 8H, $OCH_2CH_2CH_3$), 1.82 (d, J = 6.0 Hz, 24H, Me), 2.00 (tt, J = 7.2 Hz, J = 6.9 Hz, 8H, $SCH_2CH_2CH_2$), 2.58 (t, J = 7.2 Hz, 8H, $SCH_2CH_2CH_2$), 3.84 (t, J = 6.8 Hz, 8H, $OCH_2CH_2CH_3$), 4.22 (t, J = 6.9 Hz, 8H, $SCH_2CH_2CH_2$), 5.28 (hp, J = 6.0 Hz, 4H, $CHMe_2$), 7.57 (s, 4H, Ar *H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.4, 22.0, 23.0, 25.7, 33.0, 35.0, 66.0, 72.4, 118.5, 128.6, 138.8, 147.0, 149.8, 156.7, 173.2; APCI-MS (*m*/*z*) calcd for $C_{64}H_{87}N_8O_{12}S_4$ $[M + H]^+$ 1287.53; found 1287.4. Anal. Calcd for $C_{64}H_{86}N_8O_{12}S_4$: C, 59.70; H, 6.73; N, 8.70. Found: C, 59.51; H, 6.68; N, 8.60.

Crystal Data for 8: $C_{64}H_{86}N_8O_{12}S_4$, M_r = 1286.52, triclinic, $P\bar{1}$ (No. 2), a = 16.565(1) Å, b = 19.314(1) Å, c = 32.720(4) Å, α = 88.07(1)°, β = 75.55(1)°, γ = 85.94(1)°, V = 10 110(2) Å^3, Z = 6 (three crystallographically independent molecules **I**−**III** in the asymmetric unit), D_c = 1.269 g cm^{-3}, μ(Cu Kα) = 18.2 cm^{-1}, F(000) = 4116, T = 173 K; black platelike needles, 0.87 × 0.77 × 0.09 mm, Siemens P4/RA diffractometer, ω-scans, 29 450 independent reflections. The structure was solved by direct methods, and all of the non-hydrogen atoms were refined anisotropically. In each molecule the peripheral side chains exhibit disorder (very pronounced in molecule **III**), though satisfactory alternate orientations could not be located. Consequently, these parts of the molecule were allowed to assume large anisotropic thermal parameters and were refined subject to distance and angle constraints. In molecule **III**, a substantial part of the central core is also disordered, with three of the pyrrole rings adopting two discrete alternate 50:50 orientations. Refinements were by blocked full-matrix least squares based on F^2 to give R1 = 0.146 and wR2 = 0.383 for 20 871 independent observed absorption-corrected reflections ($|F_o| > 4\sigma(|F_o|)$, 2θ = 120°) and 2747 parameters.

Alternate Synthesis of 1,4,13,16-Tetrakis(1-methylethoxy)-8,9,20,21-tetrakis[(4-propyloxy-4-oxo-1-butyl)-thio]-25*H*,27*H*-dibenzo[*b*,*l*]porphyrazine (8) by Gradual Mixing. Mg turnings (0.1 g, 4.1 mmol) and I_2 (0.01 g) were added to *n*-PrOH (100 mL), and the solution was heated at reflux for 1 day under N_2. At this time the diiminoisoindoline (**4**; 2.14 g, 8.1 mmol) was dissolved in $Mg(OPr)_2$ in *n*-PrOH, and a solution of $MNT(C_4O_2Me)_2$ (**2**; 0.925 g, 2.7 mmol) in *n*-PrOH (30 mL) was added dropwise over 3 h to the stirred mixture under reflux. After the addition of $MNT(C_4O_2Me)_2$ (**2**), the reaction mixture was refluxed for an additional 4 h to complete the reaction. Workup as above gave the porphyrazines **6** (43 mg, 1%), **7** (114 mg, 3%), and **8** (348 mg, 10%).

Hydrolysis of Porphyrazines 6−8 to the Carboxylic Acid Derivatives 9−11. Excess LiOH (>4 equiv) in water was added (1:1) to a solution of porphyrazines **6**−**8** in THF. The mixed solution was stirred at room temperature for 4−5 days or until the hydrolyzed compound was completely partitioned into the lower aqueous layer, leaving a colorless upper THF layer. The aqueous layer containing the lithium salts of **9**−**11** was washed with CH_2Cl_2 and acidified with dilute HCl to precipitate the carboxylic acid derivatives **9**−**11**. The precipitated products **9**−**11** were collected by filtration and washed with a small amount of water to remove traces of HCl. In each case the hydrolysis proceeded in quantitative yield.

2,3,7,8,12,13,17,18-Octakis[(4-hydroxy-4-oxo-1-butyl)-thio]-21*H*,23*H*-porphyrazine (9): UV−vis (phosphate buffer: pH 8) λ_{max} (log ϵ) 340 (4.21), 660 (2.75), 700 (2.94) nm; ^{1}H NMR (300 MHz, pyridine-d_5) δ −1.35 (br s, 2H, N*H*), 2.62 (tt, J = 7.1 Hz, J = 7.0 Hz, 16H, $SCH_2CH_2CH_2$), 3.07 (t, J = 7.1 Hz, 16H, $SCH_2CH_2CH_2$), 4.58 (t, J = 7.0 Hz, 16H, $SCH_2CH_2CH_2$); ^{13}C NMR (75 MHz, pyridine-d_5) δ 27.1, 34.1, 35.4, 141.4, 154.0, 175.7; ESI-MS (*m*/*z*) calcd for $C_{48}H_{57}N_8O_{16}S_8$ $[M - H]^-$ 1257.17, found 1257.5. Anal. Calcd for $C_{48}H_{58}N_8O_{16}S_8$: C, 45.77; H, 4.64; N, 8.90. Found: C, 45.59; H, 4.62; N, 8.91.

19,22-Bis(1-methylethoxy)-4,5,9,10,14,15-hexakis[(4-hydroxy-4-oxo-1-butyl)thio]-23*H*,25*H*-porphyrazine (10): UV−vis (phosphate buffer: pH 8) λ_{max} (log ϵ) 340 (4.30), 666 (sh), 700 (3.47) nm; ^{1}H NMR (500 MHz, pyridine-d_5) δ −0.51 (br s, 2H, N*H*), 1.88 (d, J = 6.1 Hz, 12H, Me), 2.46 (tt, J = 6.9 Hz, J = 6.9 Hz, 4H, $SCH_2CH_2CH_2$), 2.62 (tt, J = 6.9 Hz, J = 6.9 Hz, 4H, $SCH_2CH_2CH_2$), 2.65 (tt, J = 6.9 Hz, J = 6.9 Hz, 4H, $SCH_2CH_2CH_2$), 3.00 (t, J = 6.9 Hz, 4H, $SCH_2CH_2CH_2$), 3.08 (t, J = 6.9 Hz, 4H, $SCH_2CH_2CH_2$), 3.11 (t, J = 6.9 Hz, 4H, $SCH_2CH_2CH_2$), 4.48 (t, J = 6.9 Hz, 4H, $SCH_2CH_2CH_2$), 4.67 (t, J = 6.9 Hz, 4H, $SCH_2CH_2CH_2$), 4.69 (t, J = 6.9 Hz, 4H, $SCH_2CH_2CH_2$), 5.35 (hp, J = 6.1 Hz, 2H, $CHMe_2$), 7.85 (s, 2H, Ar *H*); ^{13}C NMR (125 MHz, pyridine-d_5) δ 23.4, 27.1, 27.3, 34.0, 34.3, 35.6, 35.7, 35.9, 73.3, 120.6, 127.7, 139.0, 140.2, 143.1, 151.2, 153.8, 156.2, 175.8, 175.9, 176.0; APCI-MS (*m*/*z*) calcd for $C_{50}H_{61}N_8O_{14}S_6$ $[M + H]^+$ 1189.26, found 1189. Anal. Calcd for $C_{50}H_{60}N_8O_{14}S_6$: C, 50.49; H, 5.08; N, 9.42. Found: C, 50.27; H, 5.10; N, 9.44.

1,4,13,16-Tetrakis(1-methylethoxy)-8,9,20,21-tetrakis-[(4-hydroxy-4-oxo-1-butyl)thio]-25*H*,27*H*-dibenzo[*b*,*l*]porphyrazine (11): UV−vis (phosphate buffer: pH 8) λ_{max} (log ϵ) 334 (4.56), 658 (4.20), 798 (2.45) nm; ^{1}H NMR (500 MHz, pyridine-d_5) δ −0.68 (br s, 2H, N*H*), 1.87 (d, J = 6.0 Hz, 24H, Me), 2.74 (tt, J = 7.0 Hz, J = 7.0 Hz, 8H, $SCH_2CH_2CH_2$), 3.01 (t, J = 7.0 Hz, 8H, $SCH_2CH_2CH_2$), 4.79 (t, J = 7.0 Hz, 8H, $SCH_2CH_2CH_2$), 5.35 (hp, J = 6.0 Hz, 4H, $CHMe_2$), 7.75 (s, 4H, Ar*H*); ^{13}C NMR (125 MHz, pyridine-d_5) δ 23.5, 27.2, 34.1, 36.1, 73.2, 119.8, 129.6, 139.6, 146.7, 150.8, 158.0, 176.0; APCI-MS (*m*/*z*) calcd for $C_{52}H_{63}N_8O_{12}S_4$ $[M + H]^+$ 1119.34, found 1119. Anal. Calcd for $C_{52}H_{62}N_8O_{12}S_4$: C, 52.62; H, 5.58; N, 10.01. Found: C, 54.26; H, 5.52; N, 9.65.

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Supporting Information Available: X-ray data for **8**, including a packing diagram. This material is available free of charge via the Internet at http://pubs.acs.org.

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