

An efficient two-step synthesis of metal-free phthalocyanines using a Zn(II) template

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~ Supporting Information ~

Materials and Methods

Pyridine, pyridine-HCl, ZnCl₂, diisopropyl carbodiimide, and dicyclohexyl carbodiimide were purchased from *Fluka*, 4-nitrophthalic anhydride from *Aldrich*, and cyanamide from *Acros Organics*. All other reagents were obtained in the highest commercially available grades from *Sigma Aldrich*.

¹H-NMR spectra were measured on *Bruker ARX-300* or *AV-400* or *AV-500* spectrometers (*Bruker*, Karlsruhe, Germany). The chemical shift values are given in ppm relative to the residual signal from d₆-DMSO ($\delta = 2.50$ ppm). The coupling constants *J* are given in Hz; resonance multiplicity is described as *s* for singlet, *d* for doublet, *dd* for doublet of doublet, *t* for triplet, *m* for multiplet; and *br* is used to indicate broad signals. All data processing was carried out with *Topspin* and *Xeasy* (*Bruker*).

The mass spectra were measured by the Organic Chemistry Institute of the University of Zürich. For the matrix-assisted laser desorption/ionization (MALDI) a *Bruker* Autoflex was used. Low resolution electrospray ionization (ESI) mass spectra were measured using an Esquire LC from *Bruker*. ESI high resolution mass spectra were measured on the MAT 900 from *Finnigan*.

Visible absorbance spectra were collected using a *SpectraMax* MP5 spectrophotometer in *Greiner* Bio-one UV-Star 96-well plates (final volume = 200 μ L). IR spectra were collected using a *JASCO* FT/IR-4100 spectrometer equipped with an anvil sample compressor for matrix-free data collection. The centrifugations were performed in an *Eppendorf* Centrifuge 5804 using 50 mL polypropylene tubes.

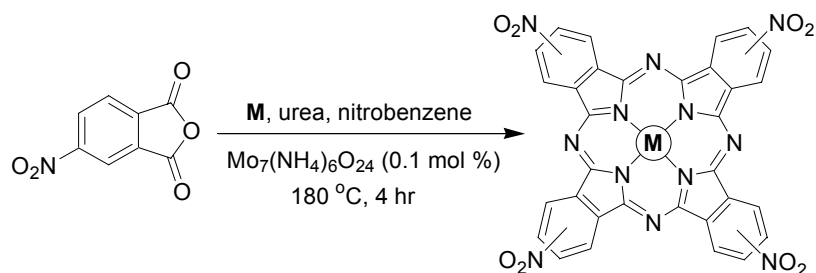
Elemental analysis was conducted by the Microanalysis Lab of the Institute of Organic Chemistry at the University of Zürich. Indicated values are the average of two or more independent measurements.

The purity of GPCs (compounds **3** – **5**) was determined by RP HPLC using a dual pump Varian (ProStar) system and a C18 Interchrom (250mm x 4.6mm; type D) reversed phase column. Products were analyzed using a gradient of acetonitrile (HPLC grade, Fisher Scientific) in water, each containing 0.1% trifluoroacetic acid (TFA).

Synthesis of Metal-Free Guanidino Phthalocyanines

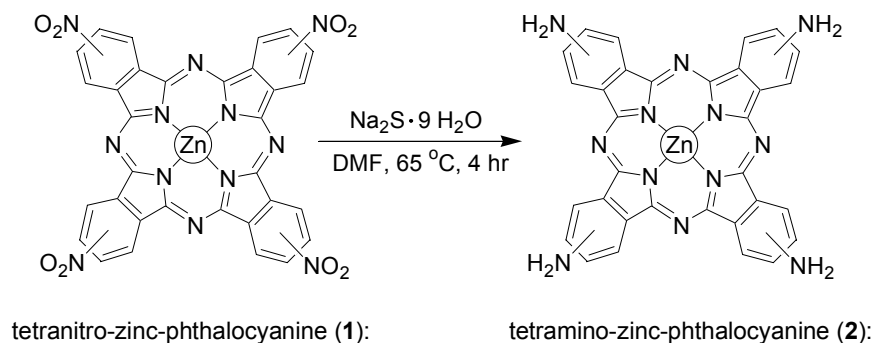
While a large number of guanidinylation methods are known,¹⁻³ common guanidinylation reagents like *N,N'*-diBoc-*N''*-(trifluoromethylsulfonyl)guanidine, and *N,N'*-diBoc-1*H*-pyrazole-1-carboxamide were not sufficiently reactive to modify the electron-poor amines of tetramino-zinc-phthalocyanine (**2**). Carbodiimides were the very first reagents used for guanidinylation,⁴ and they proved highly effective for the perguanidinylation of tetramino-zinc-phthalocyanine (**2**). The tetraguanidinium derivative **3** was synthesized by reacting **2** with 80 equivalents of cyanamide in a pyridine-HCl ionic liquid (4:1 molar ratio) at 120 °C. Including one equivalent of dimethylaminopyridine (DMAP) allowed the reaction to reach completion after 48 h. Compounds **4** and **5** did not require additional catalyst to reach completion after only 17 hours. These reactions are to our knowledge, the first examples of using a pyridine-HCl ionic liquid as a solvent and activator of guanidinylation. Evidence for complete demetallation of the GPC products **3** – **5** was initially found using ¹H NMR analysis. In d₆-DMSO, these products have broad, D₂O-exchangeable resonances at approximately –0.2 ppm that integrate to two protons. These signals are characteristic of N-H protons in the center of non-aggregated metal-free phthalocyanines.^{5,6} Additional evidence for demetallation is found in the Q-band absorbance for compounds **3** – **5**, which is split into two major transitions (see Figure SI-1, page 10). The purities of **3** – **5** were determined by RP HPLC to be ≥ 95%. High resolution ESI MS is consistent with the elemental composition of each product, and the isotope patterns observed by low resolution ESI MS matches those simulated for the metal-free products (see Figure SI-2, page 11).

Synthesis and Characterization



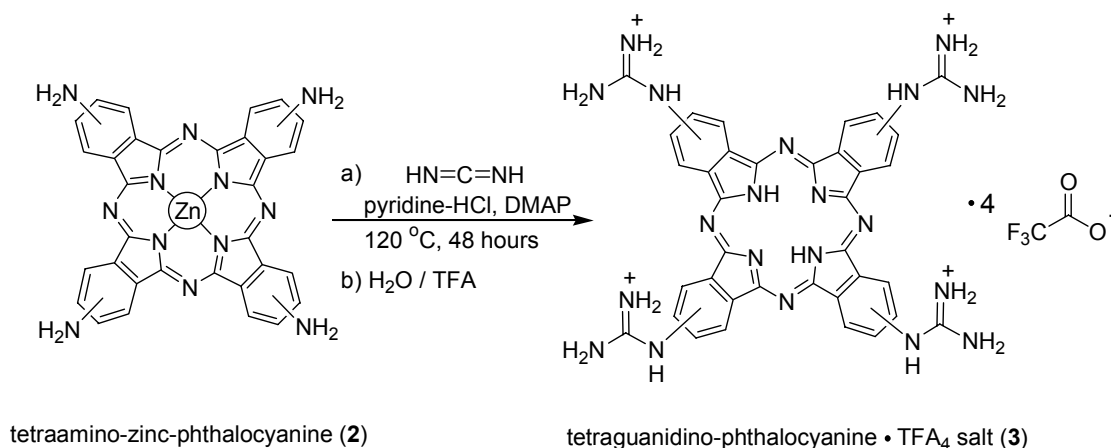
Tetranitro-metallophthalocyanines were prepared in the presence or absence of LiCl, MgCl₂, CuCl₂, or ZnCl₂ according to published procedures using nitrobenzene as a co-solvent.⁷ A representative procedure, for zinc, is included below. Reactions using the other metals were identical, except 2-fold more LiCl was used. All analytical data collected for the known compounds **1**, **2**, **6**, **7**, and **9** were consistent with those already published.^{7,8,9}

Tetranitro-zinc-phthalocyanine (1): Ammonium molybdate (13 mg, 0.01 mmol) was added to a solution of 4-nitrophthalic anhydride (2.0 g, 10 mmol), urea (3.0 g, 50 mmol), and zinc chloride (383 mg, 2.6 mmol) in nitrobenzene (15 mL). The mixture was stirred under N₂ at 185°C. After 4 h, the reaction mixture was cooled and diluted with toluene (80 mL). The resulting precipitate was collected by centrifugation. The solid was washed with toluene, water, MeOH/ether (1:9), EtOAc/hexane (2:1), and dried to afford a dark green solid (2.0 g, 98%). IR (neat, cm⁻¹): 1513, 1321, 1080, 754, 726; MALDI TOF MS (*m/z*): [M+H]⁺ calcd for C₃₂H₁₃N₁₂O₈Zn, 757.0; found 757.0.

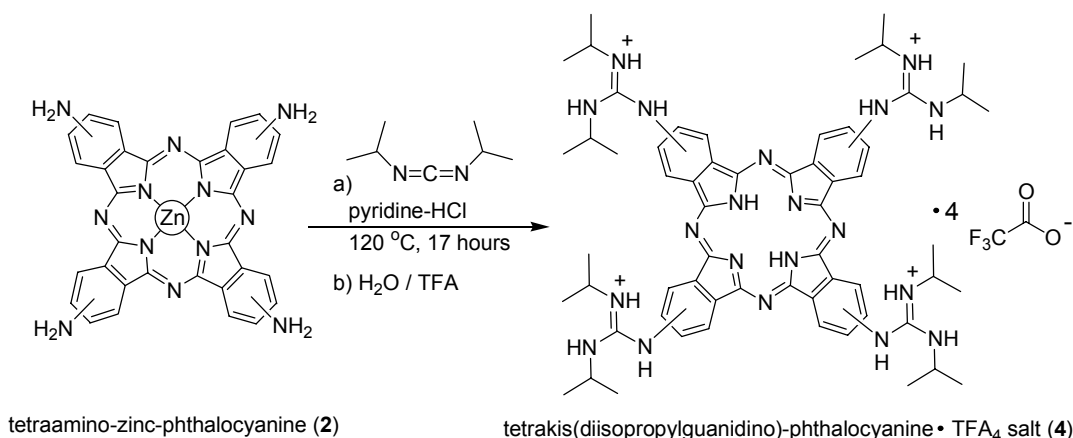


Tetraamino-zinc-phthalocyanine (2): Tetraamino-zinc-phthalocyanine (**2**) was prepared according to published procedures.⁷ Sodium sulfide nonahydrate (7.4 g, 30.9 mmol) was added to a solution of tetranitro-zinc-phthalocyanine (**1**) (1.95 g, 2.5 mmol) in DMF (50 mL). The reaction

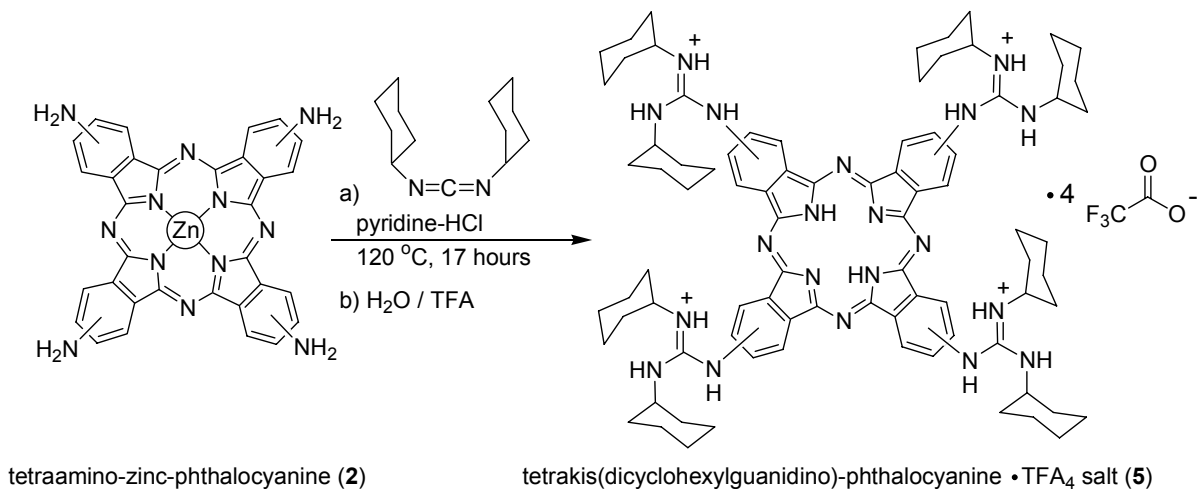
mixture was stirred under N₂ and heated at 60 °C. After 1.5 h, the mixture was cooled to room temperature, diluted with ice water (150 mL) and the resulting precipitate collected by centrifugation. The precipitate was repeatedly washed with MeOH/ether (1:9), EtOAc and dried to afford a dark green solid (1.2 g, 75%). ¹H-NMR (300 MHz, d₆-DMSO) δ 8.93 (dd, *J* = 12, 9.0 Hz, 4H), 8.42 (d, *J* = 12.0 Hz, 4H), 7.38 (d, *J* = 9.0 Hz, 4H), 6.26 (br. s, 8(NH)); IR (neat, cm⁻¹): 1603, 1490, 1344, 1092, 1044, 822, 743; MALDI TOF MS (*m/z*): [M+H]⁺ calcd for C₃₂H₂₁N₁₂Zn, 637.1; found 637.1.



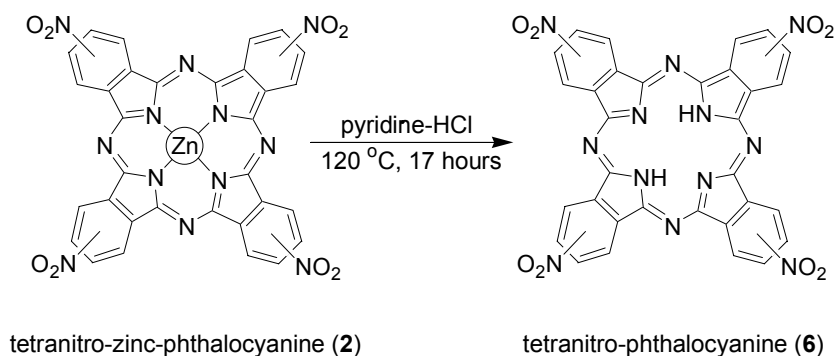
Tetraguanidino-phthalocyanine • TFA₄ salt (3): Tetramino-zinc-phthalocyanine (2) (35 mg, 0.055 mmoles), pyridine (2 mL), pyridine-HCl (1 g) and DMAP (8 mg, 0.06 mmol) were stirred under N₂ at 120 °C, and cyanamide (115 mg, 2.75 mmoles, 50 equiv) was added in three equal portions over 48 hours. The reaction was removed from the heat, and 7 mL of acetic acid was used to transfer the hot mixture into a polypropylene centrifuge tube. The resulting precipitate was collected by centrifugation at 6'500 r.p.m. and washed repeatedly with acetic acid, EtOAc, aq. NaHCO₃, and water. The dark green solid was re-dissolved in TFA (2mL) and mixed with water (5 mL). The resulting precipitate was collected by centrifugation, dissolved in a 1:3 mixture of acetonitrile and water containing 0.1% TFA (4 mL), and lyophilized to yield 46 mg (70%) of a dark green solid. ¹H-NMR (400 MHz, d₆-DMSO) δ 10.68 (br. m, 4NH), 9.55 (br. m, 4H), 9.34 (br. s, 4H), 8.24 (br. m, 4H), 8.04 (br. s, 12NH), -0.25 (br. s, 2NH); MALDI TOF MS (*m/z*): [M+H]⁺ calcd for C₃₆H₃₁N₂₀, 743.3; found 743.3; HR-ESI MS (*m/z*): [M+1]⁺ calcd for C₃₆H₃₁N₂₀ 743.3041; found 743.3037; UV-Vis (DMSO) λ_{max} (nm) and ε (cm⁻¹M⁻¹): 342 (6.0 x 10⁴), 677 (9.9 x 10⁴), and 704 (1.0 x 10⁵).



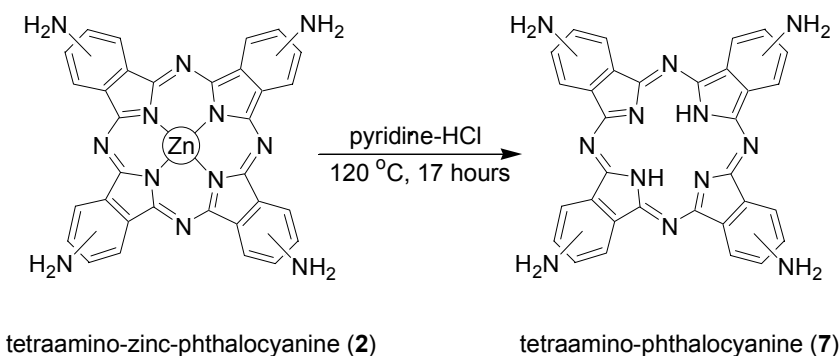
Tetrakis(diisopropylguanidino)-phthalocyanine • TFA₄ salt (4): Tetramino-zinc-phthalocyanine (2) (35 mg, 0.055 mmoles), pyridine (2 mL), pyridine-HCl (1 g), and diisopropylcarbodiimide (400 μ L, 2.6 mmoles, 47 equiv) were stirred under N₂ at 120 °C for 17 h. The reaction was removed from the heat, and 10 mL of H₂O was used to transfer the hot mixture into a polypropylene centrifuge tube. TFA (1.2 mL) was added, mixed, and the resulting precipitate was collected by centrifugation at 6'500 r.p.m. The supernatant was removed and mixed with TFA (1 mL), centrifuged, and the supernatant discarded. The combined precipitates were sonicated with 0.1 N NaCl (7 mL) and then mixed with TFA (1.2 mL), centrifuged, and the colorless supernatant was carefully removed. The resulting precipitate was sonicated in water (7 mL) and then mixed with TFA (1.2 mL), and the precipitate collected as before. The precipitate was dissolved in TFA (2mL) and mixed with water (7 mL). The resulting precipitate was collected by centrifugation, dissolved in a 1:3 mixture of acetonitrile and water containing 0.1% TFA (4 mL), and lyophilized to yield 70 mg (83%) of a dark green solid. ¹H-NMR (400 MHz, d₆-DMSO) δ 10.33 (s, 2NH), 10.29 (s, 2NH), 9.54 (d, J = 3 Hz, = 2H), 9.51 (d, J = 3 Hz = 2H), 9.28 (s, 2H), 9.15 (s, 2H), 8.35 (br. s, 8NH), 8.18 (m, 4H), 4.23 (m, 8H), 1.40 (m, 48H), -0.15 (br. s, 2NH); MALDI TOF MS (m/z): [M+H]⁺ calcd for C₆₀H₇₉N₂₀, 1079.7; found 1079.6; HR-ESI MS (m/z): [M+H]⁺ calcd for C₆₀H₇₉N₂₀, 1079.6797; found 1079.6798; UV-Vis (DMSO) λ_{max} (nm) and ϵ (cm⁻¹M⁻¹): 347 (5.4 x 10⁴), 682 (8.49 x 10⁴), and 710 (9.24 x 10⁴).



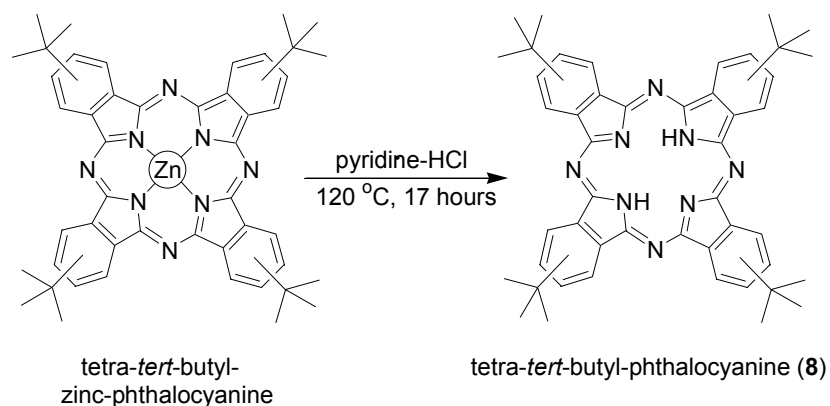
Tetrakis(dicyclohexylguanidino)-phthalocyanine • TFA₄ salt (5): Tetraamino-zinc-phthalocyanine (**2**) (35 mg, 0.055 mmol), pyridine (2 mL), pyridine-HCl (1 g), and dicyclohexylcarbodiimide (227 mg, 1.1 mmol, 20 equiv) were stirred under N₂ at 120 °C for 17 h. The reaction was removed from the heat and 5 mL of H₂O was used to transfer the hot mixture into a polypropylene centrifuge tube, the resulting precipitate was collected by centrifugation at 6'500 r.p.m. and washed repeatedly with hot water (3 mL) and centrifuged. The dark green solid was dissolved in acetonitrile (10 mL) and filtered. The filtrate was evaporated and passed over a C18 reversed phase column (3:5, acetonitrile:water, containing 0.1% TFA). Evaporation of the solvent yielded 75 mg (74%). ¹H-NMR (400 MHz, d₆-DMSO) δ 10.32 (br. s, 2NH), 10.30 (br. s, 2NH), 9.51 (t, *J* = 8.6 Hz, 2H), 9.40 (t, *J* = 8.0 Hz, 2H), 9.30 (s, 2H), 9.15 (br. s, 2H), 8.35 (m, 8NH), 8.19 (br. s, 2H), 8.17 (br. s, 2H), 3.33 (m, 8H), 2.13 (m, 16H), 1.84 (m, 16H), 1.65 (m, 8H), 1.52 (m, 16H), 1.39 (m, 16H), 1.17 (m, 8H), -0.14 (br. s, 2NH); MALDI TOF MS (*m/z*): [M+H]⁺ calcd for C₈₄H₁₁₁N₂₀, 1399.9; found 1399.8. HR-ESI (*m/z*): [M+1]⁺ calcd for C₈₄H₁₁₀N₂₀, 1399.9301; found 1399.9303; UV-Vis (DMSO) λ_{max} (nm) and ε (cm⁻¹M⁻¹): 347 (5.2 × 10⁴), 682 (8.56 × 10⁴), and 710 (9.69 × 10⁴).



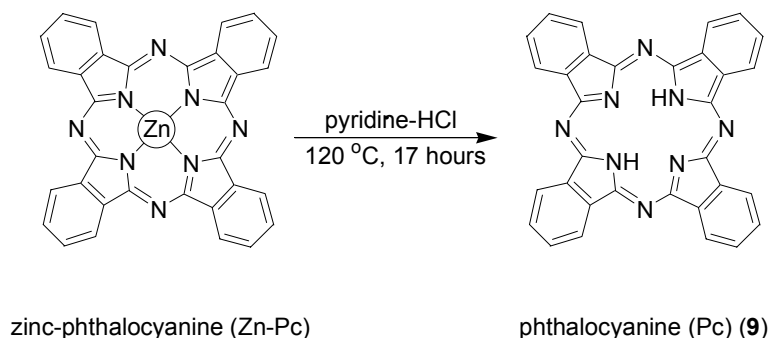
Tetranitro-phthalocyanine (6): Tetranitro-zinc-phthalocyanine (**2**) (35 mg, 0.046 mmoles), pyridine (2 mL), and pyridine-HCl (1 g) were stirred under N₂ at 110 °C for 17 h. The reaction was removed from the heat, and 10 mL of H₂O was used to transfer the hot mixture into a polypropylene centrifuge tube. The resulting precipitate was collected by centrifugation at 6'500 r.p.m. The dark green precipitate was washed repeatedly with H₂O, MeOH, and dried under high vacuum to yield 26 mg (81%). IR (neat, cm⁻¹): 3096, 1523, 1338, 1134, 1005, 841, 776, 734; MALDI TOF MS (*m/z*): [M+H]⁺ calcd for C₃₂H₁₅N₁₂O₈, 695.1; found 695.2. Elemental analysis C₃₃H₁₈N₁₂O₉ (·CH₃OH) calc: C 54.55, H 2.50, N 23.13; found: C 54.84, H 2.48, N 23.4%.



Tetraamino-phthalocyanine (7). Tetraamino-zinc-phthalocyanine (**2**) (35 mg, 0.055 mmoles), pyridine (2 mL), and pyridine-HCl (1 g) were stirred under N₂ at 110 °C for 17 h. The reaction was removed from the heat and 10 mL of H₂O was used to transfer the hot mixture into a polypropylene centrifuge tube. The resulting precipitate was collected by centrifugation at 6'500 r.p.m. The dark green precipitate was washed repeatedly with H₂O, MeOH, EtOAc, and dried under high vacuum to yield 30.2 mg (95%). ¹H-NMR (400 MHz, d₆-DMSO) δ 8.95 (m, 4H), 8.43 (br. s, 2H), 8.38 (d, *J* = 8 Hz, 2H), 7.45 (m, 4H), 6.5 (br. s, 8NH), 0.40 (br. m, 2NH); IR (neat, cm⁻¹): 3285, 3079, 1610, 1531, 1435, 1020, 815, 803, 704; MALDI TOF MS (*m/z*): [M]⁺ calcd for C₃₂H₂₂N₁₂, 574.2; found 574.2.

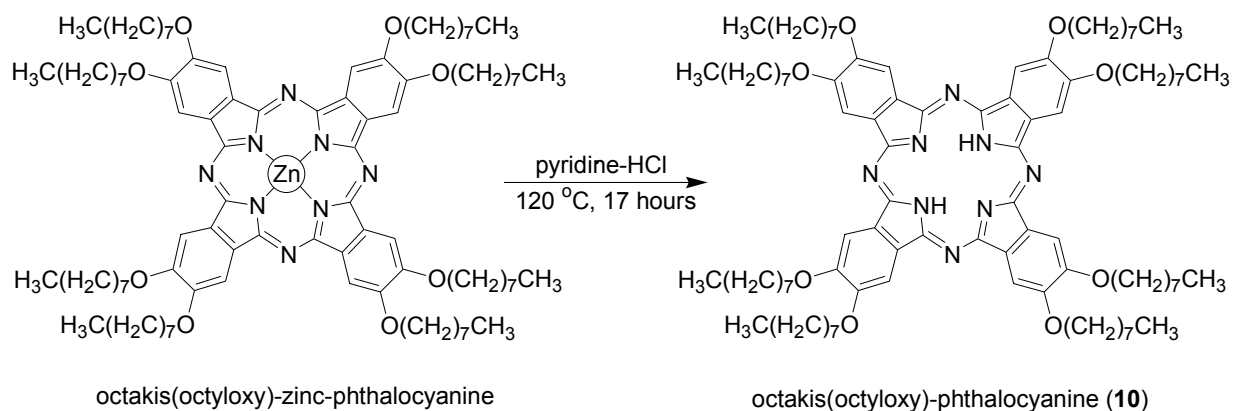


Tetra-*tert*-butyl-phthalocyanine (8). Tetra-*tert*-butyl-zinc-phthalocyanine (94 mg, 0.11 mmoles), pyridine (5 mL), and pyridine-HCl (2.5 g) were stirred under N₂ at 120°C for 17 h. The reaction was removed from the heat, and water (10 mL) was added while the reaction was still hot and the mixture allowed to cool. The resulting precipitate was collected by centrifugation at 6'500 r.p.m. The dark blue precipitate was washed repeatedly with H₂O, MeOH, and dried under high vacuum to yield 69 mg (80%). IR (neat, cm⁻¹): 3291, 2954, 2365, 1616, 1482, 1392, 1258, 1090, 892, 826, 746; MALDI TOF MS (*m/z*): [M] calcd for C₄₈H₅₀N₈, 738.4; found 738.3; Elemental analysis C₄₈H₅₀N₈ calcd: C 78.02, H 6.82, N 15.16; found: C 78.15, H 6.85, N 15.12%; UV-Vis (CHCl₃) λ max (nm) and ε (cm⁻¹M⁻¹): 340 (8.33 x 10⁴), 665 (1.29 x 10⁵), 700 (1.51 x 10⁵).



Phthalocyanine (Pc) (9). Zinc-phthalocyanine (190 mg, 0.329 mmoles), pyridine (10 mL), and pyridine-HCl (5 g) were stirred under N₂ at 120 °C for 17 h. The reaction was removed from the heat, and water (10 mL) was added while the reaction was still hot. The resulting precipitate was collected by centrifugation at 6'500 r.p.m. The dark green-blue precipitate was washed with water (20 mL), ethanol (20 mL), acetone (20 mL), and dried to yield 155 mg of product (91 %).

IR (neat, cm^{-1}): 3272, 1500, 1436, 1333, 1321, 1117, 1093, 1001, 779, 750, 728, 718; MALDI TOF MS (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{32}\text{H}_{19}\text{N}_8$, 515.2; found 515.2; Elemental analysis $\text{C}_{32}\text{H}_{18}\text{N}_8$ calc: C 74.70, H 3.53, N 21.78; found: C 74.37, H 3.57, N 21.54%; Visible absorbance see Figure SI-1 A).



Octakis(octyloxy)-phthalocyanine (10). Octakis(octyloxy)-zinc-phthalocyanine (50 mg, 0.031 mmoles), pyridine (2 mL), and pyridine-HCl (1 g) were stirred under N_2 at 120C for 17 h. The reaction was removed from the heat, and water (10 mL) was added while the reaction was still hot and the mixture allowed to cool. The resulting precipitate was collected by centrifugation at 6'500 r.p.m. The dark green precipitate was washed repeatedly with H_2O , MeOH, and dried under high vacuum to yield 41 mg (85%). IR (neat, cm^{-1}): 3287, 2981, 2850, 2361, 2336, 1611, 1449, 1381, 1272, 1199, 1099, 1019, 853, 744; MALDI TOF MS (m/z): $[\text{M}]$ calcd for $\text{C}_{96}\text{H}_{146}\text{N}_8\text{O}_8$, 1539.1; found 1539.0; Elemental analysis $\text{C}_{96}\text{H}_{146}\text{N}_8\text{O}_8$ calcd: C 74.86, H 9.55, N 7.28; found: C 74.68, H 9.44, N 7.28%; UV-Vis (CHCl_3) λ max (nm) and ϵ ($\text{cm}^{-1}\text{M}^{-1}$): 344 (8.4×10^4), 665 (1.19×10^5), 704 (1.32×10^5)

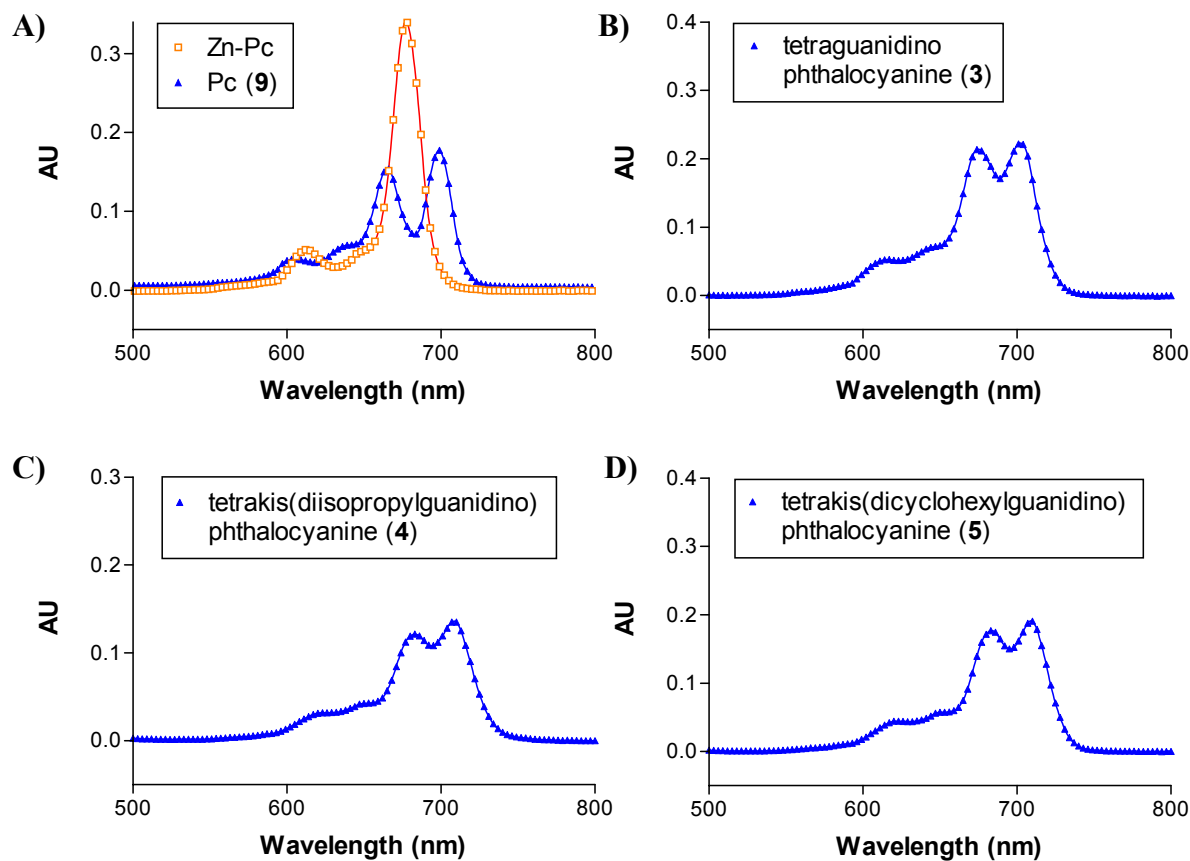


Figure SI-1. Visible absorbance spectra of: **A)** 1.1 μM solutions of zinc phthalocyanine (Zn-Pc) and the isolated metal-free phthalocyanine product (9) in 1-bromonaphthylene. These spectra match reported standards.⁹ **B)** 2.1 μM solution of tetraguanidino-phthalocyanine \cdot TFA₄ salt (3) in 0.1% TFA / DMSO; **C)** 1.4 μM solution of tetrakis(diisopropylguanidino)-phthalocyanine \cdot TFA₄ salt (4) in 0.1% TFA / DMSO; and **D)** 2.0 μM solution of tetrakis(dicyclohexylguanidino)-phthalocyanine \cdot TFA₄ salt (5) in 0.1% TFA / DMSO. Under these conditions, all absorbance spectra obey the Beer–Lambert law over a range of 0.3 – 10 μM .

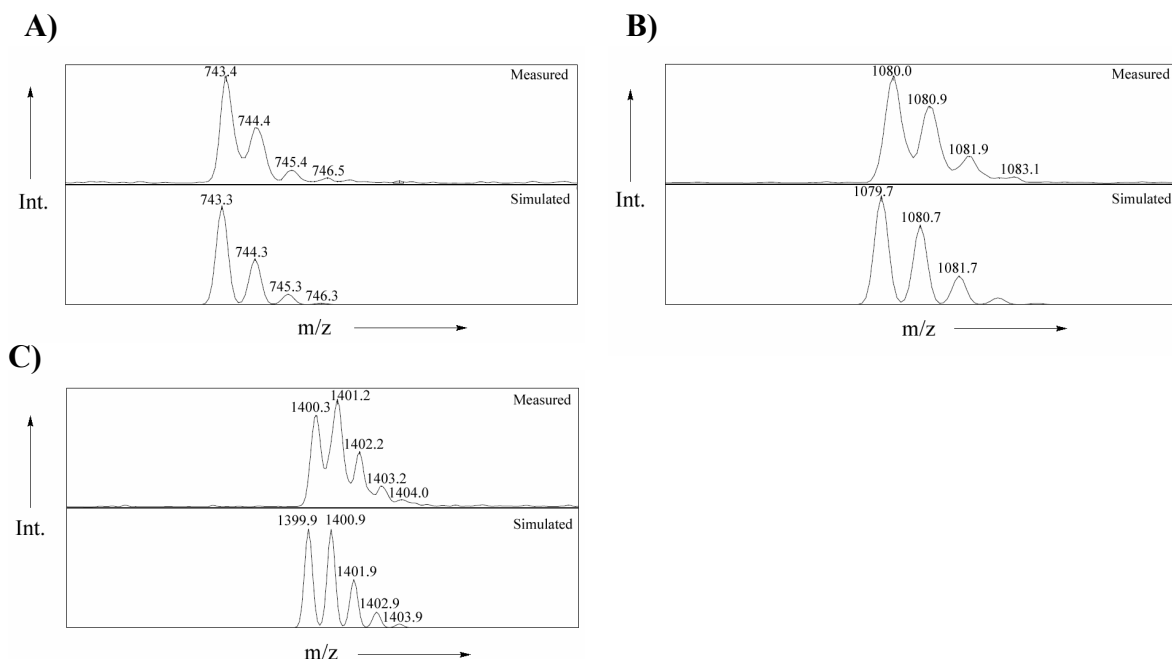


Figure SI-2. Isotope patterns according to low resolution ESI MS for **A)** tetraguanidino phthalocyanine · TFA₄ salt (**3**); **B)** tetrakis(diisopropylguanidino)-phthalocyanine · TFA₄ salt (**4**); and **C)** tetrakis(dicyclohexylguanidino)-phthalocyanine · TFA₄ salt (**5**). High resolution ESI MS gave results consistent with the expected molecular formulas of **3 – 5**.

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